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(54) Title: MENTHOL SUBSTITUTED ANTITHROMBOTIC PAI-1 INHIBITORS

(57) Abstract: This invention is directed to menthol-substituted compounds and their pharmaceutically acceptable salts which are useful as antithrombotic agents by inhibiting plasminogen activator inhibitor-1 (PAI-1). In addition, the present invention relates to pharmaceutical compositions and their pharmaceutically acceptable salts, containing the menthol substituted compounds, derivatives of the menthol substituted compounds, and methods of using the compounds to treat disease-states characterized by thrombotic activity.

MENTHOL SUBSTITUTED ANTITHROMBOTIC PAI-1 INHIBITORS

Field of the Invention

The present invention relates to menthol-substituted compounds and their pharmaceutically acceptable salts that are useful as antithrombotic agents by inhibiting plasminogen activator inhibitor-1 (PAI-1). In addition, the present invention relates to pharmaceutical compositions and their pharmaceutically acceptable salts containing the menthol substituted compounds, derivatives of the menthol substituted compounds, and methods of use.

Background of the Invention

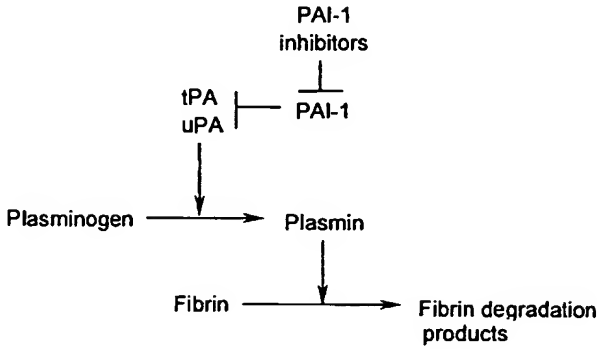
Thrombotic diseases remain a major health care problem despite the tremendous progress made in understanding the molecular mechanisms of blood coagulation and pathogenesis of thrombosis and atherosclerosis. In fact, each year in the United States, approximately 1.5 million patients experience acute myocardial infarction and 5 million patients develop angina.

Generally, thrombosis occurs from an imbalance between prothrombotic and antithrombotic mechanisms. In principle, either enhanced platelet activation and blood coagulation or reduced fibrinolytic activity could lead to thrombosis. Currently marketed antithrombotic drugs and the majority in development are designed to inhibit platelets or blood coagulation factors. Thrombolytic agents, such as streptokinase, and recombinant tissue-type plasminogen activator (tPA) and urokinase (uPA) are used mostly for acute myocardial infarction. These protein-based drugs are designed to be administered intravenously for rapid onset of action.

PAI-1 is the major negative regulator of tPA and uPA in the fibrinolytic system. High levels of PAI-1 reduce fibrinolytic potential and contribute to the development of thrombosis. Recent studies have demonstrated the feasibility of using small molecular weight nonpeptide compounds to inhibit PAI-1 activity and promote fibrinolysis *in vivo*. In addition to thrombosis, PAI-1 may also play a role in other pathological settings such as chemotherapy-induced pulmonary fibrosis and cancer progression.

Fibrinolysis is a physiological mechanism designed to remove intravascular thrombus maintaining vascular patency. After a blood clot is formed in an injured vessel, the fibrinolytic system degrades the fibrin clot, restoring blood flow to vital organs and tissues. The

fibrinolytic system consists of several proteases, namely tPA and uPA and plasminogen, which form a enzymatic cascade in which tPA and uPA convert plasminogen to plasmin which in turn degrades fibrin, as follows:



The fibrinolytic enzymes of the fibrinolytic system are not only physiologically important in vascular homeostasis but can also cause unwanted effects such as bleeding and excessive vascular proteolysis. Therefore, tight regulation of the fibrinolytic system is of homeostatic importance. Under physiological conditions, regulation is typically achieved by activation of zymogens through limited proteolysis, controlled binding of plasminogen or plasmin to fibrin, and inactivation of proteases by serine protease inhibitors, as shown above.

PAI-1 is the principal negative regulator of tPA and uPA in the fibrinolytic system. The PAI-1 gene is located on chromosome 7q21.3-q22. The protein consists of 379 amino acids and has a molecular weight of 52kDa. As a member of the serine protease inhibitor (serpin) superfamily, PAI-1 protein folds into a conserved tertiary structure consisting of three beta-sheets, nine alpha-helices and a reactive center loop. PAI-1 inhibits tPA and uPA through its reactive center loop that mimics the substrate sequence of the target proteases. The reaction results in the formation of an irreversible complex of the protease and inhibitor, thereby inhibiting the activities of the enzymes.

PAI-1 is synthesized by vascular endothelial cells, hepatocytes and smooth muscle cells and can range in concentration in human plasma between about 0.5 to 1.5 nmol/L. Functionally, there are two forms of PAI-1: an active form and an inactive or latent form. Only the active form binds to tPA and uPA, and inhibits their activities. PAI-1 is typically released from cells in active form, but is rapidly converted to the latent form through a conformational change. This conformational change prevents the interaction of PAI-1 with tPA or uPA.

PAI-1 as a thrombotic risk factor is well documented in several studies. Elevated levels of plasma PAI-1 are associated with a variety of thrombotic diseases including deep vein thrombosis, disseminated intravascular coagulation (DIC), unstable angina, premature myocardial infarction, coronary artery disease, and atherosclerosis. In patients with recent onset unstable angina, subsequent cardiovascular events such as acute myocardial infarction and severe recurrent angina correlated closely with increased plasma PAI-1 activity. In addition, high levels of plasma PAI-1 are also reported in other metabolic diseases that are associated with increased thrombotic risk, such as obesity, noninsulin-dependent diabetes, hyperinsulinemia, and hypertriglyceridemia. Further, PAI-1 is also implicated in cancer progression and invasion. High levels of PAI-1 have been reported in a variety of human tumors including neuroblastoma, colorectal carcinoma, head and neck squamous cell carcinoma, breast carcinoma, gastric cancer, and ovarian cancer. The expression was often associated with large, invasive tumors, metastatic tumors, and drug resistant tumors.

Thrombolytic therapy using known agents, such as antiplatelet and anticoagulant drugs, have presented a major challenge in reducing angiographic reocclusion. In fact, angiographic reocclusion is observed in about 30% of patients three months after successful thrombolysis for acute myocardial infarction. Reocclusion significantly affects recovery of left ventricular function and leads to a poorer long-term clinical outcome. Other approaches are therefore necessary to reduce coronary reocclusion.

A number of polyclonal and monoclonal antibodies against PAI-1 have been developed. The anti-thrombotic effects of anti-PAI-1 antibodies are well documented in various animal models. For example, infusion of anti-human PAI-1 antibody reduced plasma PAI-1 activity and inhibited intravascular thrombus formation, as demonstrated by a dose-dependent decrease in fibrin deposition in the lungs of rats having endotoxin induced thrombosis. Studies with PAI-1 antibodies suggest the PAI-1 inhibitors could be used in combination with antiplatelet and anticoagulant drugs to prevent coronary reocclusion after thrombolytic therapy.

In addition, several drugs have been reported that inhibit PAI-1 secretion or production in endothelial cells. Fibrates, for example, are a class of compounds widely used to lower plasma cholesterol and triglycerides in hyperlipidemic patients. In addition, Raloxifene and Tamoxifen, estrogen derived compounds developed to treat osteoporosis and breast cancer, were shown to inhibit PAI-1 secretion induced by IL-1 in estrogen-activated human umbilical vein endothilial cells.

A major drawback to the above-identified drugs is that they inhibit PAI-1 production or secretion by endothelial cells. The molecular mechanism controlling PAI-1 synthesis and secretion may vary in different cells, and therefore would be difficult to develop a specific drug that directly inhibits the production of PAI-1 in the variety of cells. An alternative approach is to develop a drug that directly inhibits PAI-1 activity, instead. A drug that inhibits PAI-1 activity has immediate antithrombotic effects once present in the blood.

To date, several small molecules have been identified that directly inhibit human PAI-1 activity. For example, compounds derived from microbial metabolites, such as diketopiperazine-based compounds, were found to inhibit PAI-1 activity. In amidolytic assays, these compounds inhibited PAI-1 activity with IC_{50} values ranging from 3.5 to 80 μM. However, it is not clear whether these compounds directly block PAI-1 binding to tPA or convert active PAI-1 to latent PAI-1.

In addition, another small molecule PAI-1 inhibitor has been developed from flufenamic acid. Further, a series of benzothiophenobenzofuran- and indole-based small molecules have been identified that inhibit PAI-1 activity. Although recent progress has demonstrated the feasibility of developing a small molecule PAI-1 inhibitor, most reported PAI-1 inhibitor compounds have an IC_{50} value in the micromolar range. Further chemical modifications are clearly needed to improve the potency of these compounds.

In addition to small molecules that directly inhibit PAI-1 activity, other molecules were reported to inhibit PAI-1 production. In general, these molecules are neither potent nor specific. For example, in tissue culture, gemfibrozil (100μM) suppressed basal PAI-1 production from human umbilical vein endothelial cells by 15% and attenuated the augmentation of PAI-1 synthesis induced by growth factors, such as EGF, TGF-B and platelet lysates. Similar effects of gemfibrozil were also observed on PAI-1 synthesis by cultured hepatocytes (HepG2), although effective concentrations required for gemfibrozil were much higher (750μM). When administered in rabbits, both gemfibrozil and niacin inhibited PAI-1 mRNA expression in the liver and reduced plasma PAI-1 concentrations in the animals. In other studies, attempts were made to use antisens oligonucleotides to block PAI-1 production in human endothelial cells or smooth muscle cells. It is very unlikely that an anti-PAI-1 drug for chronic use could be developed based on an antisens strategy.

More recently, Vingradsky et al. reported another compound, (3E, 4E)-3-benzylidene-4-(3,4,5-trimethoxy-benzylidene)-pyrrolidine-2,5-dione (T-686), as a novel PAI-1 inhibitor. In

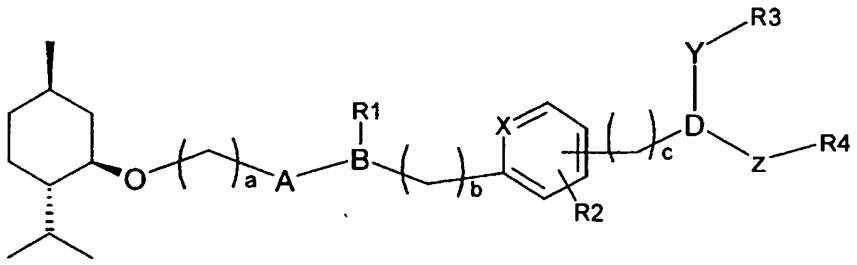
cultured human umbilical vein endothelial cells, T-686 (10μM) reduced basal production of PAI-1 by 32%. T-686 also attenuated TGF-B induced PAI-1 expression in these cells. In hypercholesterolemic rabbits, oral administration of T-686 (30mg/kg/day) lowered plasma PAI-1 levels and reduced atherosclerotic lesion area by 19%. These studies support the concept that inhibition of PAI-1 is a useful therapeutic strategy for prevention of atherothrombotic diseases.

Therefore, a class of compounds is needed in pharmaceutical mixtures that inhibits the activity of PAI-1 *in vivo* that overcomes the problems associated with prior compounds. In addition, a class of compounds is necessary that has increased potency at smaller dosages than the compounds known in the prior art to prevent thrombosis, atherosclerosis, fibrosis, such as, but not limited to, idiopathic and drug-induced pulmonary fibrosis, hepatic fibrosis and systemic sclerosis, and may further be utilized to prevent cancer invasion and chemotherapy-induced fibrosis.

Summary of the Invention

The present invention relates to antithrombotic molecules that act as PAI-1 inhibitors in fibrinolysis and are therefore useful as pharmacological agents for the treatment of disease states characterized by thrombotic activity. Specifically, the present invention relates to menthol substituted compounds and their pharmaceutically acceptable salts that are useful as antithrombotic agents that inhibit PAI-1 in fibrinolysis.

To this end, in an embodiment of the present invention, the invention provides compounds selected from the group consisting of the following formula:



wherein:

a, b, and c is 0 to 2;

A is either absent or present and is either carbonyl or forms a heterocyclic ring system with B (if B is N) and the phenyl group;

B is either absent or present and is selected from the group consisting of N or O;

R1 is either absent or present and is selected from the group consisting of hydrogen, alkyl, alkylene, aryl, haloalkyl, menthoxy alkyl, or forms a heterocyclic ring system with the B (if B is N) and the phenyl (preferably forming an optionally substituted indole);

R2 is selected from the group consisting of hydrogen, alkoxy, amino, monoalkylaminocarbonyl, monoalkylaminocarbonyl carboxylic acid, nitro, alkyl, haloalkyl, substituted aralkoxy (substituted with carboxylic acid), alkoxy substituted phenyl amido, cyclohexyloxybenzoylamino, or a fused [1,3]dioxinyl ring system;

X is either C or N;

D is either absent or present and is either O or N;

Y is either absent or present and is selected from alkylene, optionally substituted aryl, carbonyl, or forms a heterocyclic ring system with D (if D is N) and the phenyl ring;

Z is either absent or present and is selected from the group consisting of alkylene, aryl, sulfonyl, aminocarbonyl, or carbonyl;

R3 is either absent or present and is selected from the group consisting of optionally substituted phenyl (optionally substituted by hydrogen, nitro, hydroxy, and/or alkoxy), carboxylic acid, alkoxy, alkyl or carbamate ester; and

R4 is either absent or present and is selected from the group consisting of optionally substituted dibenzo[b,e][1,4]dioxepin-11-one (wherein said phenyl groups of said dioxepinone are optionally substituted by hydroxy, alkyl, carboxylic acid, and alkoxy), optionally substituted pyridinyl (optionally substituted by carboxylic acid and/or alkylene), naphthalene, optionally substituted phenyl (optionally substituted by one or more of hydroxy, carboxylic acid, nitro, alkyl, alkoxy, carboxylic acid substituted alkoxy, alkyl ester, acetic acid, acetic acid ether, amido, amino, alkoxyamido, methanesulfonyl amino, halo, tetrazolyl, optionally substituted aralkoxy (optionally substituted by hydroxy, carboxylic acid, nitro, alkyl, alkoxy, tetrazolyl), optionally substituted aryloxy (optionally substituted one or more times by hydroxy, carboxylic acid, nitro, alkyl, alkoxy, tetrazolyl, carboxylic acid substituted alkoxy, alkyl ester, amino, halo, or aryloxy), carboxylic acid substituted phenyl ester, optionally substituted piperazinyl (optionally substituted by carboxylic acid or carboxylic acid substituted alkoxy, alkyl ester), optionally substituted pyridinyloxy (optionally substituted by carboxylic acid, carboxylic acid alkyl ester, or cyano), carboxylic acid substituted cyclohexyl, or optionally substituted fully saturated monocyclic aza ring with up to six carbon atoms (optionally substituted by carboxylic acid alkyl ester or carboxylic acid)), alkoxy, carboxylic acid

substituted cyclohexane, or carboxylic acid substituted fully saturated monocyclic aza ring with up to six carbon atoms; or

R3 and R4 form a carboxylic acid substituted fully saturated monocyclic aza ring with up to 6 carbon atoms,

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another aspect, this invention provides compositions useful in treating a human having a disease-state characterized by thrombotic activity, which composition comprises a therapeutically effective amount of a compound of the invention as described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another aspect, this invention provides a method of treating a human having a disease-state characterized by thrombotic activity, which method comprises administering to a human in need thereof a therapeutically effective amount of a compound of the invention as described above.

In another aspect, this invention provides a method of treating a human having a disease-state alleviated by the inhibition of plasminogen activator inhibitor-1 (PAI-1), which method comprises administering to a human in need thereof a therapeutically effective amount of a compound of the invention as described above.

In another aspect, this invention provides a method of inhibiting plasminogen activator inhibitor-1 (PAI-1) in vitro or in vivo by the administration of a compound of the invention.

Detailed Description of the Presently Preferred Embodiments

A. Definitions

As used in the specification and/or the appended claims, unless specified to the contrary, the following terms have the meaning indicated:

"Alkyl" refers to a straight or branched chain monovalent or divalent radical consisting solely of carbon and hydrogen, containing no unsaturation and having from one to six carbon atoms, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl), and the like.

"Alkoxy" refers to a radical of the formula $-OR_a$, where R_a is alkyl as defined above, e.g., methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, n-pentoxy, 1,1-dimethylethoxy (t-butoxy), and the like.

"Alkylene" refers to a straight or branched chain divalent radical consisting of carbonyl and hydrogen, containing no unsaturation and having from one to six carbon atoms, e.g., methylene, ethylene, propylene, n-butylene, and the like.

"Aryl" refers to a phenyl or naphthyl radical.

"Aralkyl" refers to a radical of the formula $-R_aR_b$ where R_a is alkyl as defined above, and R_b is aryl as defined above, e.g., benzyl.

"Aryloxy" refers to a radical of the formula -ORb where Rb is aryl as defined above, e.g., benzyloxy, and the like.

"Dialkylamino" refers to a radical of the formula -NRaRa where each Ra is independently an alkyl radical as defined above, e.g., diethylamino, methylethylamino, diethylamino, dipropylamino, ethylpropylamino, and the like.

"Dialkylaminocarbonyl" refers to a radical of the formula -C(O)NRaRa where each Ra is independently an alkyl radical as defined above, e.g., diethylaminocarbonyl, dipropylaminocarbonyl, ethylpropylaminocarbonyl, and the like.

"Halo" refers to bromo, chloro, iodo or fluoro.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, e.g., trifluoromethyl, difluoromethyl, trichloromethyl, 2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like.

"Haloalkoxy" refers to a radical of the formula $-OR_f$, where R_f is haloalkyl as defined above, e.g., 2-trifluoromethoxy, difluoromethoxy, trichloromethoxy, 2-trifluoroethoxy, 1-fluoromethyl-2-fluoroethoxy, 3-bromo-2-fluoropropoxy, 1-bromomethyl-2-bromoethoxy, and the like.

"Heterocyclic ring system" refers to a stable 3- to 15-membered ring radical which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur. For purposes of this invention, the heterocyclic ring system may be monocyclic, bicyclic, or tricyclic ring systems, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclic ring system radical may be optionally oxidized; the nitrogen atom may be optionally quatermized; and the ring system may be partially or fully saturated or aromatic. The heterocyclic ring system radical may be attached to the main structure at any heteroatom or carbon which results in the creation of a stable structure. Examples of such heterocyclic ring system radicals include, but are not limited

to, aziridinyl, azetidinyl, piperidinyl, piperazinyl, 2-oxo-piperazinyl, 2-oxopiperidinyl, 2-oxo-pyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolinyl, pyrrolidinyl, imidazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, triazolyl, indanyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolinyl, octahydroisoindolinyl, quinolinyl, dihydroquinolinyl, tetrahydroquinolinyl, isoquinolinyl, decahydroisoquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, bezimidazolyl, thidiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, benzoxalyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 2-azabicylco[2,2,2]heptyl and oxadiazolyl.

"Menthoxy" refers to a radical of 2-isopropyl-5-methyl-cyclohexyloxy. Menthoxy may be in any of two forms: (+)-menthoxy, or (-)-menthoxy. Compounds of the present invention preferably utilize (-)-menthoxy, although (+)-menthoxy should not be excluded from the present invention.

"Monoalkylamino" refers to a radical of the formula -NHRa where Ra is an alkyl radical as defined above, e.g., methylamino, ethylamino, propylamino, and the like.

"Monoalkylaminocarbonyl" refers to a radical of the formula -C(O)NHRa where Ra is an alkyl radical as defined above, e.g., methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, and the like.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitutions.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids, such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid,

mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betamine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline and caffeine.

"Rt" refers to room temperature.

"Therapeutically effective amount" refers to that amount of a compound of formula (I) which, when administered to a human in need thereof, is sufficient to effect treatment, as defined below, for disease-states characterized by thrombotic activity. The amount of a compound of formula (I) which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease-state and its severity, and the age of the human to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

"Treating" or "treatment" as used herein cover the treatment of a disease-state in a human, which disease-state is characterized by thrombotic activity, and include:

(i) preventing the disease-state from occurring in a human, in particular, when such human is predisposed to the disease-state but has not yet been diagnosed as having it;

(ii) inhibiting the disease-state, i.e., arresting its development; or

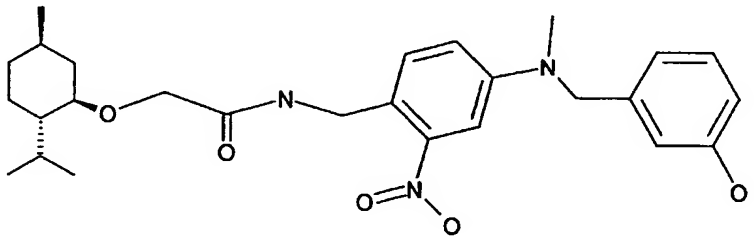
(iii) relieving the disease-state, i.e., causing regression of the disease-state.

The disease state may comprise unstable angina, myocardial infarction, cerebral thromboembolism, transient ischemic attack, stroke, DVT, and coronory reocclusion after thrombolytic therapy, as well as others.

The yield of each of the reactions described herein is expressed as a percentage of the theoretical yield.

The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms, oxidized sulfur atoms or quaternized nitrogen atoms in their structure. The compounds of the invention and their pharmaceutically acceptable salts may therefore exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of this invention.

The nomenclature used herein is a modified form of the I.U.P.A.C. system wherein the compounds of the invention are named as derivatives of menthoxy, as defined above. For example, a compound of the invention selected from formula I wherein a is 1, b is 1, c is 0, A is carbonyl, B is N, R1 is H, R2 is nitro and is substituted at the ortho position of the phenyl ring, D is N and is substituted at the para position of the phenyl ring, Y is absent, R3 is methyl, Z is methylene, and R4 is hydroxy substituted phenyl, i.e.,



is named herein as N-{4-[(3-Hydroxy-benzyl)-methyl-amino]-2-nitro-benzyl}-2-(menthoxy)-acetamide.

B. Utility

The compounds of the present invention are inhibitors of PAI-1 and therefore useful in disease-states characterized by thrombotic activity based on PAI-1's role in inhibiting fibrinolysis (see Background of the Invention above). A primary indication for the compounds is prophylaxis of deep vein thrombosis (DVT), disseminated intravascular coagulation (DIC), unstable angina, premature myocardial infarction, subsequent cardiovascular events such as acute myocardial infarction, coronary artery disease, and atherosclerosis. The compounds of the present invention may also be useful for indications of increased thrombotic risk, such as

obesity, noninsulin-dependent diabetes, hyperinsulinemia, and hypertriglyceridemia. The compounds of the present invention may also be used in treating diseases characterized by fibrosis, such as, but not limited to, idiopathic and drug-induced pulmonary fibrosis, hepatic fibrosis and systemic sclerosis. The compounds of the present invention may also be useful in treating cancer progression and invasions, such as neuroblastoma, colorectal carcinoma, head and neck squamous cell carcinoma, breast carcinoma, gastric cancer and ovarian cancer.

Each compound listed herein has been demonstrated to inhibit the activity of PAI-1 either by an *in vitro* or an *in vivo* assay or both. Specifically, the present compounds have been demonstrated to have IC_{50} values of less than about 15μM.

C. Testing

To screen small molecule PAI-1 inhibitors of the present invention, a chromogenic *in vitro* assay was developed in which human PAI-1 activity is measured by inhibition of uPA-dependent substrate hydrolysis. In this assay, human uPA (30nM), and human recombinant PAI-1 (8nm)) were incubated in a reaction mixture containing 50nM Tris-HCl (pH=7.5), 140 nM NaCl, 2.5 nM $CaCl_2$ and 0.1% polyethylene glycol (PEG). The activity of uPA was determined by the initial rate of cleavage of a peptide substrate (S2444, Glu-Gly-Arg-pNA; Diapharma). The cleavage product, p-nitroaniline, was measured by monitoring IR absorbance at 405 nm.

Additionally, an *in vivo* fibrin clot lysis assay was developed. The fibrin clot lysis assay was used to evaluate the potency of small molecule PAI-1 inhibitors. In this assay, pooled human plasma was diluted (1:3) in a buffer containing 150 nM NaCl, 2 nM $CaCl_2$, 20 mM Hepes, pH 7.4. Fibrin clot formation was initiated by the addition of human thrombin (30 nM). The newly formed fibrin clot remained stable at 37°C for at least two hours. If exogenous human tPA (4 nM) was included in the assay, the clot would be lysed within 20 minutes at 37°C, which has a monitored optical absorbance at 405 nm. In the presence of recombinant human or rat PAI-1 (4.3 nM), the activity of tPA was reduced and clot lysis time was delayed. When both PAI-1 and PAI-1 inhibitors were added, the PAI-1 activity was significantly inhibited, as demonstrated by shorted clot lysis times. The inhibition of PAI-1 by small molecule compounds was dose dependent. The IC_{50} values were determined for each compound. In control studies, PAI-1 inhibitors did not affect the tPA-dependent clot lysis in the absence of PAI-1 under the same experimental conditions.

D. General Administration

Administration of the compounds of the present invention in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be administered, for example, orally, nasally, parenterally, topically, transdermally, or rectally, in the form of a solid, semi-solid, lyophilized powder or liquid dosage forms, such as via tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc.

Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention and 99% to about 1% by weight of a suitable pharmaceutical excipient. Preferably, the composition will be about 5% to about 75% by weight of a compound(s) of the invention with the rest being suitable pharmaceutical excipients.

The preferred route of administration is oral, using a convenient daily dosage regimen which can be adjusted according to the degree of severity of the disease state to be treated. For such oral administration, a pharmaceutically acceptable composition containing a compound(s) of the invention is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, pregelatinized starch, magnesium stearate, sodium saccharine, talcum, cellulose ether derivatives, glucose, gelatin, sucrose, citrate, propyl gallate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations, and any other like excipient that may be apparent to one having ordinary skill in the art.

Preferably, such compositions will take the form of capsule, caplet, or tablet and therefore will also contain a diluent such as lactose, sucrose, dicalcium phosphate, and other like diluents; a disintegrant such as croscarmellose sodium or derivatives thereof; a lubricant such as magnesium stearate and other like lubricants; and a binder such as starch, gum acacia, polyvinylpyrrolidine, gelatin, cellulose ether derivatives, and other like lubricants.

The compounds of the present invention may also be formulated into a suppository using, for example, about 0.5% to about 50% active ingredient disposed in a carrier that slowly

dissolves within the body. For example, typical carrier materials may be polyethylene glycol (PEG), PEG 1000 (96%) and PEG 4000 (4%).

Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. a compound(s) of the invention (about 5% to about 20%), and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and other like carriers, to form a solution or suspension.

If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, and antioxidants, such as citric acid, sorbitan monolaurate, triethanolamine oleate, butylated hydroxytoluene, etc.

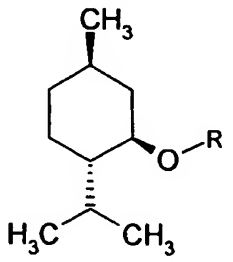
Actual methods of preparing such dosage forms are known and are apparent, to those skilled in the art. For example, see *Remington's Pharmaceutical Sciences*, 18th Ed., (Mack Publishing Co., Easton, Pennsylvania, 1990). The composition to be administered will contain a therapeutically effective amount of a compound of the invention for treatment of a disease state alleviated by the inhibition of PAI-1 in fibrinolysis, in accordance with the teachings of this invention.

The compounds of the present invention are administered in a therapeutically effective amount which will vary depending upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states and the host undergoing therapy. Generally, a therapeutically effective daily does is from about 0.14 mg to about 14.3 mg/kg of body weight per day of a compound of the present invention. Preferably, the pharmaceutical composition includes from about 0.7 mg to about 10 mg/kg of body weight per day. For example, for administration to a 70 kg person, the dosage would be about 10mg to about 1.0 gram per day of a compound of the invention. More preferably, the pharmaceutical composition includes about 50 mg to about 700 mg per day of a compound of the present invention. Most preferably, the pharmaceutical composition includes about 100 mg to about 500 mg per day of a compound of the present invention.

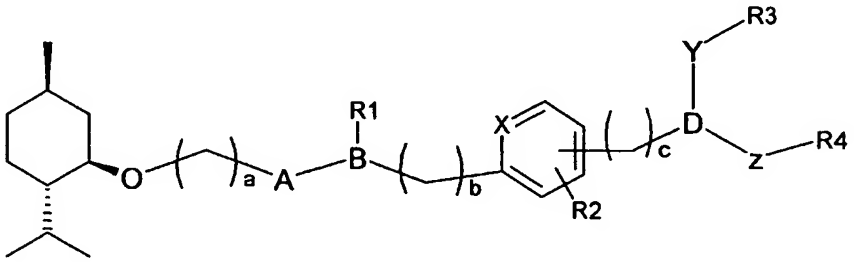
E. Compounds as PAI-1 inhibitors

Preferred Embodiments

The present invention relates to compounds having substituted menthoxy groups. More specifically, the present invention relates to substituted menthoxy groups as shown below:



A preferred group of compounds having the general substituted menthoxy structure as noted above is that group wherein the compounds are selected from formula (I), as shown below:



Formula I

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof.

A preferred subgroup of this group is that subgroup of compounds wherein a, b, and c is 0 to 2;

A is either absent or present and is either carbonyl or forms a heterocyclic ring system with the B (if B is N) and the phenyl (preferably forming benzimidazolyl);

B is either absent or present and is selected from the group consisting of N or O;

R1 is absent or present and is selected from the group consisting of hydrogen, alkyl, alkylene, aryl, haloalkyl, menthoxy alkyl, or forms a heterocyclic ring system with B (if B is N) and the phenyl (preferably forming an optionally substituted indole);

R2 is selected from the group consisting of hydrogen, alkoxy, amino, monoalkylaminocarbonyl, monoalkylaminocarbonyl carboxylic acid, nitro, alkyl, haloalkyl, substituted aralkoxy (substituted with carboxylic acid), cyclohexyloxybenzoylamino, or a fused [1,3]dioxinyl ring system or [1,4]dioxinyl ring system with the phenyl;

X is either C or N;

D is absent or present and is either O or N;

Y is either absent or present and is selected from alkylene, aryl, carbonyl, or forms a heterocyclic ring system with D and the phenyl ring (preferably forming an optionally substituted benzimidazolyl or an optionally substituted indole);

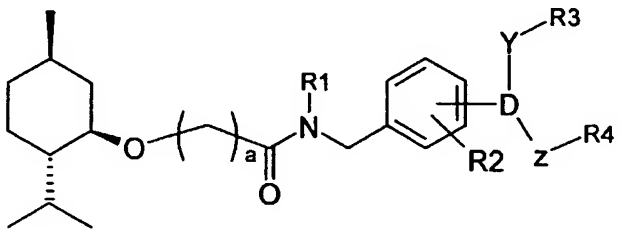
Z is either absent or present and is selected from the group consisting of alkylene, aryl, sulfonyl, aminocarbonyl, or carbonyl;

R3 is either absent or present and is selected from the group consisting of hydrogen, optionally substituted phenyl (optionally substituted by nitro, hydroxy, and/or alkoxy), optionally substituted aralkyl (optionally substituted by nitro and hydroxy), carboxylic acid, alkoxy, or alkyl; and

R4 is either absent or present and is selected from the group consisting of optionally substituted dibenzo[b,e][1,4]dioxepin-11-one (wherein said phenyl groups of said dioxepinone are optionally substituted by hydroxy, alkyl, carboxylic acid, and alkoxy), optionally substituted pyridinyl (optionally substituted by carboxylic acid and/or alkylene), naphthalene, optionally substituted phenyl (optionally substituted by one or more of hydroxy, carboxylic acid, nitro, alkyl, alkoxy, carboxylic acid substituted alkoxy, alkyl ester, acetic acid, acetic acid ether, amido, amino, alkoxyamido, methanesulfonylamino, halo, tetrazolyl, optionally substituted aralkoxy (optionally substituted by hydroxy, carboxylic acid, nitro, alkyl, alkoxy, tetrazolyl), optionally substituted aryloxy (optionally substituted one or more times by hydroxy, carboxylic acid, nitro, alkyl, alkoxy, tetrazolyl, carboxylic acid substituted alkoxy, alkyl ester, amino, halo, or aryloxy), carboxylic acid substituted phenyl ester, optionally substituted piperazinyl (optionally substituted by carboxylic acid or carboxylic acid substituted alkoxy, alkyl ester), optionally substituted pyridinyloxy (optionally substituted by carboxylic acid, carboxylic acid alkyl ester, or cyano), carboxylic acid substituted cyclohexyl, or optionally substituted fully saturated monocyclic aza ring with up to six carbon atoms (optionally substituted by carboxylic acid alkyl ester or carboxylic acid)), alkoxy, carboxylic acid substituted cyclohexane, or carboxylic acid substituted fully saturated monocyclic aza ring with up to six carbon atoms, or

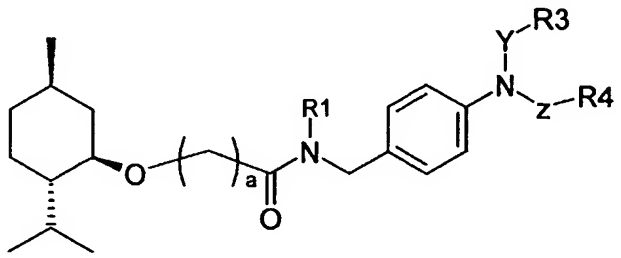
R3 and R4 form a carboxylic acid substituted fully saturated monocyclic aza ring with up to 6 carbon atoms.

A preferred subgroup of compounds is that subgroup of compounds of Formula I wherein a is 0 or 1; b is 1, c is 0; A is carbonyl; B is N; X is C; and R1, R2, R3, R4, D, Y and Z are as described above. This preferred subgroup of compounds is, therefore, selected from compounds of the following Formula IA:



Formula IA

A preferred subclass of Formula IA is that group of compounds of Formula IA wherein R2 is hydrogen and D is N, as shown below in Formula IA1:



Formula IA1

wherein a is 0 or 1;

R1 is hydrogen, alkyl, alkylene, or forms a five member ring structure with the nitrogen and the phenyl to form a substituted indole;

Y is absent or present and is selected from the group consisting of hydrogen or methylene;

R3 is absent or present and is selected from the group consisting of hydrogen, alkyl, optionally substituted aralkyl (optionally substituted by one or more of hydroxy or nitro), and carboxylic acid;

Z is either absent or present and is selected from the group consisting of methylene, sulfonyl, aminocarbonyl, and carbonyl; and

R4 is either absent or present and is selected from the group consisting of optionally substituted dibenzo[b,e][1,4]dioxepin-11-one (wherein said phenyl groups of said dioxepinone are optionally substituted by hydroxy, alkyl, carboxylic acid, and alkoxy), optionally

substituted pyridinyl (optionally substituted by carboxylic acid and/or alkylene), naphthalene, optionally substituted phenyl (optionally substituted by one or more of hydroxy, carboxylic acid, nitro, alkyl, alkoxy, carboxylic acid substituted alkoxy, alkyl ester, acetic acid, acetic acid ether, amido, amino, alkoxyamido, methanesulfonyl amino, halo, tetrazolyl, optionally substituted aralkoxy (optionally substituted by hydroxy, carboxylic acid, nitro, alkyl, alkoxy, tetrazolyl), optionally substituted aryloxy (optionally substituted one or more times by hydroxy, carboxylic acid, nitro, alkyl, alkoxy, tetrazolyl, carboxylic acid substituted alkoxy, alkyl ester, amino, halo, or aryloxy), carboxylic acid substituted phenyl ester, optionally substituted piperazinyl (optionally substituted by carboxylic acid or carboxylic acid substituted alkoxy, alkyl ester), optionally substituted pyridinyloxy (optionally substituted by carboxylic acid, carboxylic acid alkyl ester, or cyano), carboxylic acid substituted cyclohexyl, or optionally substituted fully saturated monocyclic aza ring with up to six carbon atoms (optionally substituted by carboxylic acid alkyl ester or carboxylic acid)), alkoxy, carboxylic acid substituted cyclohexane, or carboxylic acid substituted fully saturated monocyclic aza ring with up to six carbon atoms.

Particularly preferred compounds of this class of compounds are selected from the following:

3-Hydroxy-4-{4-[2-menthoxy-acetylamino]-piperidin-1-ylmethyl}-8-methoxy-1,9-dimethyl-11-oxo-11H-dibenzo[b,e][1,4]dioxepine-6-carboxylic acid;

3-[4-({Allyl-[2-menthoxy-acetyl]-amino}-methyl)-phenylsulfamoyl]-benzoic acid;

N-{4-[Bis-(2-hydroxy-5-nitro-benzyl)-amino]-benzyl}-2-menthoxy-acetamide;

2-Menthoxy-N-(4-{(2-hydroxy-5-nitro-benzyl)-[2-(2-hydroxy-5-nitro-benzyloxy)-5-nitro-benzyl]-amino}-benzyl)-acetamide;

N-{4-[Bis-(2-hydroxy-5-nitro-benzyl)-amino]-benzyl}-2-menthoxy-acetamide;

[(2-Hydroxy-3-hydroxymethyl-5-nitro-benzyl)-(4-{[2-menthoxy-acetylamino]-methyl}-phenyl)-amino]-acetic acid;

N-{4-[(2-Hydroxy-5-nitro-benzyl)-(methyl)-amino]-benzyl}-2-menthoxy-acetamide;

2-(2-{[(2-Hydroxy-5-nitro-benzyl)-(4-{[2-menthoxy-acetylamino]-methyl}-phenyl)-amino]-methyl}-6-methoxy-phenoxy)-5-nitro-benzoic acid;

N-{4-[(2-Hydroxy-5-nitro-benzyl)-methyl-amino]-benzyl}-2-menthoxy-acetamide;

2-(2-{[(2-Hydroxy-3-methoxy-benzyl)-(4-{[2-menthoxy-acetylamino]-methyl}-phenyl)-amino]-methyl}-6-methoxy-phenoxy)-5-nitro-benzoic acid;

N-(4-{[2-(2-Hydroxy-5-nitro-benzyloxy)-5-nitro-benzyl]-(methyl)-amino}-benzyl)-2-menthoxy-acetamide;

4-(2-{[(4-{[2-Menthoxy-acetylamino]-methyl}-phenyl)-methyl-amino]-methyl}-4-nitro-phenoxymethyl)-benzoic acid;

3-Hydroxy-4-[(4-{[2-menthoxy-acetylamino] methyl}-phenylamino)-methyl]-8-methoxy-1,9-dimethyl-11-oxo-11H-dibenzo[b,e][1,4]dioxepine-6-carboxylic acid;

N-[4-(2-Hydroxy-5-nitro-benzylamino)-benzyl]-2-menthoxy-acetamide;

4-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-benzoic acid;

4-[3-(4-{[2-Menthoxy-acetylamino]-methyl}-phenyl)ureido]-benzoic acid ethyl ester;

{2-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-4-nitro-phenoxy}-acetic acid;

2-Hydroxy-3-[(4-{[2-menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-benzoic acid;

2-Menthoxy-N-[4-(2,4,5-trihydroxy-benzylamino)-benzyl]-acetamide;

{3-Amino-4-[(4-{[2-menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-phenoxy}-acetic acid;

{4-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-phenyl}-acetic acid;

N-[4-(4,5-Dihydroxy-2-nitro-benzylamino)-benzyl]-2-(menthoxy)-acetamide;

{3-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-phenoxy}-acetic acid;

N-[4-(2-Hydroxy-3,5-dinitro-benzylamino)-benzyl]-2-menthoxy-acetamide;

N-[4-(2-Hydroxy-5-nitro-benzylamino)-benzyl]-2-(menthoxy)-acetamide;

N-{4-[(2-Hydroxy-5-nitro-phenylamino)-methyl]-benzyl}-2-menthoxy-acetamide;

[4-(2-Hydroxy-5-nitro-benzylamino)-benzyl]-carbamic acid-menthoxy ester;

5-{2-[3-(4-{[2-Menthoxy-acetylamino]-methyl}-phenyl)-ureido]-4-methoxycarbonyl-phenoxy}-isophthalic acid dimethyl ester;

4-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-benzo[1,3]dioxole-2,2-dicarboxylic acid methyl ester;

2-{2-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-phenoxy}-5-methoxy-benzoic acid;

2-{2-Carbamoyl-5-hydroxy-6-[(4-{[2-menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-3-methyl-phenoxy}-3-hydroxy-5-methoxy-4-methyl-benzoic acid;

2-{3-Fluoro-2-[(4-{[2-menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-phenoxy}-5-methoxy-benzoic acid;

2-{2-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-4-nitro-phenoxy}-4-phenoxy-benzoic acid;

2-{2-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-6-methoxy-phenoxy}-5-nitro-benzoic acid;

3-{3-Fluoro-2-[(4-{[2-menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-phenoxy}-2-hydroxy-benzoic acid;

2-Menthoxy-N-(4-{5-nitro-2-[4-(1H-tetrazol-5-yl)-benzyloxy]-benzylamino}-benzyl)-acetamide;

5-Amino-2-{2-[(4-{[2-menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-6-methoxy-phenoxy}-benzoic acid;

N-[1-(2-Hydroxy-5-nitro-benzyl)-2,3-dihydro-1H-indol-5-yl]-2-menthoxy-acetamide;

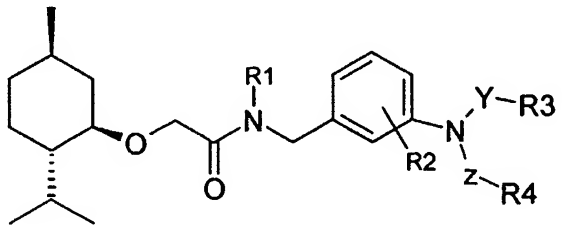
(4-{(2-Hydroxy-5-nitro-benzyl)-[2-(2-hydroxy-5-nitro-benzyloxy)-5-nitro-benzyl]-amino}-benzyl)-carbamic acid 2-isopropyl-5-methyl-cyclohexyl ester;

{4-[Bis-(2-hydroxy-5-nitro-benzyl)-amino]-benzyl}-carbamic acid menthoxy ester;

{4-[Bis-(2-hydroxy-5-nitro-benzyl)-amino]-benzyl}-carbamic acid (+)-menthoxy ester;

(4-{(2-Hydroxy-5-nitro-benzyl)-[2-(2-hydroxy-5-nitro-benzyloxy)-5-nitro-benzyl]-amino}-benzyl)-carbamic acid (+)menthoxy ester.

Another preferred subclass of Formula IA is that group of compounds of the following Formula IA1, as follows:



Formula IA2

wherein R1 is hydrogen or aralkyl;

R2 is hydrogen or carboxylic acid substituted benzyloxy, or a fused [1,3]dioxinyl ring system or [1,4]dioxinyl ring system with the phenyl ;

Y is absent or present and is selected from the group consisting of hydrogen or methylene;

R3 is absent or present and is selected from the group consisting of hydrogen, and optionally substituted aryl (optionally substituted by one or more of hydroxy, nitro, and carboxylic acid);

Z is either absent or present and when present is methylene;

R4 is either absent or present and is selected from the group consisting of optionally substituted dibenzo[b,e][1,4]dioxepin-11-one (wherein said phenyl groups of said dioxepinone are optionally substituted by hydroxy, alkyl, carboxylic acid, and alkoxy), and optionally substituted phenyl (optionally substituted by one or more of hydroxy, carboxylic acid, nitro, alkoxy and optionally substituted aryloxy (optionally substituted by hydroxy and nitro).

Particularly preferred compounds of this class of compounds are selected from the following:

3-Hydroxy-4-[(3-{[2-menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-8-methoxy-1,9-dimethyl-11-oxo-11H-dibenzo[b,e][1,4]dioxepine-6-carboxylic acid;

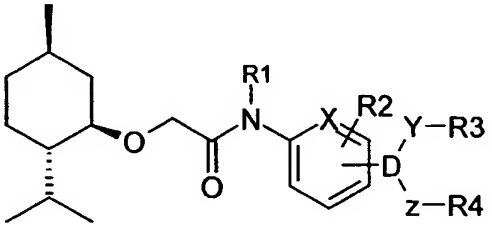
N-{6-[Bis-(2-hydroxy-5-nitro-benzyl)-amino]-4H-benzo[1,3]dioxin-8-ylmethyl}-2-menthoxy-acetamide;

N-(6-{(2-Hydroxy-5-nitro-benzyl)-[2-(2-hydroxy-5-nitro-benzyloxy)-5-nitro-benzyl]-amino}-4H-benzo[1,3]dioxin-8-ylmethyl)-2-menthoxy-acetamide;

4-[2-({Benzyl-[2-menthoxy-acetyl]amino}-methyl)-4-nitrophenoxymethyl]-benzoic acid;

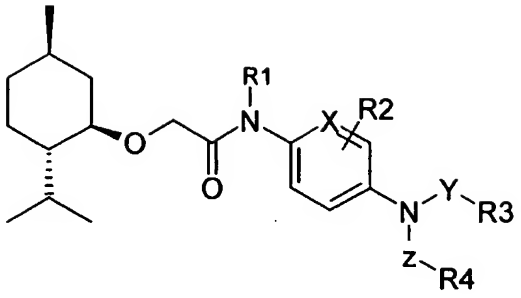
N-[6-(2-Hydroxy-5-nitro-benzylamino)-4H-benzo[1,3]dioxin-8-ylmethyl]-2-menthoxy-acetamide.

Another preferred subgroup of Formula I is that group of compounds wherein a is 1, b and c are 0, and D, X, Y, Z, R1, R2, R3 and R4 are as described above, as follows:



Formula IB

A preferred subclass of Formula IB is that subclass of compounds wherein D is N, having the following formula:



Formula IB1

wherein R1 is hydrogen or forms a five member ring structure with the nitrogen and the phenyl to form a substituted indole;

X is either C or N;

R2 is selected from the group consisting of hydrogen, alkoxy, amino, monoalkylaminocarbonyl, monoalkylaminocarbonyl carboxylic acid, nitro, alkyl, and optionally substituted aralkoxy (optionally substituted with carboxylic acid);

Y is either absent or present and is selected from the group consisting of hydrogen, methylene, carbonyl or forms a 5 member heterocyclic ring system with the N and the phenyl ring to form a substituted indole or substituted benzoimidazole;

R3 is absent or present and is selected from the group consisting of hydrogen, alkyl, optionally substituted aryl (optionally substituted by one or more of hydroxy or nitro), carboxylic acid and alkyl ether;

Z is either absent or present and is selected from the group consisting of alkylene, optionally substituted aryl, and carbonyl;

R4 is either absent or present and is selected from the group consisting of hydrogen, optionally substituted pyridinyl (optionally substituted by carboxylic acid, alkylene), naphthalene, optionally substituted phenyl (optionally substituted by one or more of hydrogen, hydroxy, carboxylic acid, nitro, alkyl, alkoxy, carboxylic acid substituted alkoxy, alkyl ester, acetic acid, acetic acid ether, amido, amino, alkoxy amido, methanesulfonylamino, halo, tetrazolyl, optionally substituted aralkoxy (optionally substituted by hydroxy, carboxylic acid, nitro, alkyl, alkoxy, tetrazole), optionally substituted aryloxy (optionally substituted by hydrogen, hydroxy, carboxylic acid, nitro, alkyl, alkoxy, tetrazolyl, carboxylic acid substituted alkoxy, alkyl ester, amino, halo, and aryloxy), carboxylic acid substituted phenyl ester, optionally substituted piperazine (optionally substituted by carboxylic acid or carboxylic acid alkyl ester), optionally substituted pyridinyloxy (optionally substituted by carboxylic acid,

carboxylic acid alkyl ester, or cyano), carboxylic acid substituted cyclohexyl, optionally substituted fully saturated monocyclic aza ring with up to six carbon atoms (optionally substituted by carboxylic acid alkyl ester or carboxylic acid)), menthoxy alkyl, or carboxylic acid substituted cyclohexane.

Particularly preferred compounds of this class of compounds are selected from the following:

N-[5-(2-Hydroxy-5-nitro-benzylamino)-pyridin-2-yl]-2-menthoxy-acetamide;

2-Menthoxy-N-(4-{(2-hydroxy-5-nitro-benzyl)-[2-(2-hydroxy-5-nitro-benzyloxy)-5-nitro-benzyl]-amino}-phenyl)-acetamide;

3,4,5,6-Tetrafluoro-N-{4-[2-menthoxy-acetylamino]-phenyl}-phthalamic acid;

N-[4-(2-Hydroxy-5-nitro-benzylamino)-2-methoxy-phenyl]-2-menthoxy-acetamide;

N-{4-[Bis-(2-hydroxy-5-nitro-benzyl)-amino]-2-methoxy-phenyl}-2-menthoxy-acetamide;

1-{5-[Bis-(2-hydroxy-5-nitro-benzyl)-amino]-2,3-dihydro-indol-1-yl}-2-menthoxy-ethanone;

N-[1-(2-Hydroxy-5-nitro-benzyl)-2,3-dihydro-1H-indol-5-yl]-2-menthoxy-acetamide;

4-({4-[2-Menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-benzoic acid;

2-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-phenylamino}-methyl)-phenoxy]-benzoic acid;

2-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-phenylamino}-methyl)phenoxy]-3-methoxy-benzoic acid;

4-({4-[2-Menthoxy-acetylamino]-2,5-dimethoxy-phenylamino}-methyl)-benzoic acid;

4-({4-[2-(Menthoxy)-acetylamino]-5-methoxy-2-methyl-phenylamino}-methyl)-benzoic acid;

4-{2-(3-Carboxy-propionylamino)-5-[2-menthoxy-acetylamino]-phenoxy}-benzoic acid methyl ester;

2-Hydroxy-3-({4-[2-menthoxy-acetylamino]-5-methoxy-2-methylphenylamino}-methyl)-benzoic acid;

2-[2-({4-[2-Menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-methoxy-phenoxy]-nicotinic acid;

6-[2-({4-[2-Menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-methoxy-phenoxy]-nicotinic acid;

1-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-nitro-phenyl]-piperidine-3-carboxylic acid;

5-Bromo-2-[3-fluoro-2-({4-[2-menthoxy-acetylamino]-phenylamino}-methyl)-phenoxy]-benzoic acid;

4-{2-Acetylamino-5-[2-menthoxy-acetylamino]-phenoxy}-benzoic acid;

1-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-nitro-phenyl]-pyrrolidine-2-carboxylic acid methyl ester;

4-{2-Ethoxycarbonylamino-5-[2-menthoxy-acetylamino]-phenoxy}-benzoic acid;

1-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-nitro-phenyl]-pyrrolidine-2-carboxylic acid methyl ester;

1-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-nitro-phenyl]-pyrrolidine-2-carboxylic acid;

4-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-nitro-phenoxy]-benzoic acid;

1-[6-Amino-3-fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-phenyl]-piperidine-4-carboxylic acid;

4-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-4-nitro-phenoxy]-benzoic acid;

1-{4-Ethoxycarbonylamino-2-[(ethoxycarbonyl-{4-[2-menthoxy-acetylamino]-3-methoxy-phenyl}-amino)-methyl]-3-fluoro-phenyl}-piperidine-4-carboxylic acid;

1-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-methanesulfonylamino-phenyl]-piperidine-4-carboxylic acid;

4-[2-({4-[2-Menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-3-methoxy-6-nitro-phenoxy]-3,5-dimethoxy-benzoic acid;

6-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-nitro-phenoxy]-nicotinic acid;

1-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-phenyl]-piperidine-4-carboxylic acid;

4-Chloro-2-[2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-methoxy-phenoxy]-benzoic acid;

4-Acetyl-1-{2-[(acetyl-{4-[2-menthoxy-acetylamino]-3-methoxy-phenyl}-amino)-methyl]-3-fluoro-6-nitro-phenyl}piperazine-2-carboxylic acid;

4-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-nitro-phenyl]-piperazine-1,3-dicarboxylic acid 1-methyl ester;

6-[4-Fluoro-5-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-2-nitro-phenoxy]-pyridine-2-carboxylic acid methyl ester;

1-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-methoxycarbonylamino-phenyl]-piperidine-4-carboxylic acid;

6-Fluoro-2-[2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-methoxy-phenoxy]-3-nitro-benzoic acid;

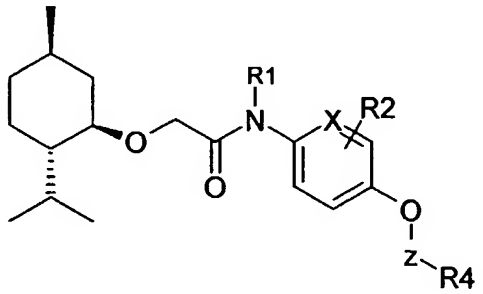
4-{2,4-Bis-[2-menthoxy-acetylamino]-3-phenoxy}-benzoic acid;

5-Chloro-2-[2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-methoxy-phenoxy]-3-nitro-benzoic acid;

4-{5-[2-Menthoxy-acetylamino]-2-methyl-benzoimidazol-1-ylmethyl}-benzoic acid;

N-[4-(2-Hydroxy-5-nitro-benzylamino)-phenyl]-2-menthoxy-acetamide.

Another preferred subclass of Formula IB is that group of compounds wherein D is oxygen, and Z, R1, R2 and R4 are as described above. This preferred subclass can generally be represented by formula IB2, as follows:



Formula IB2

wherein R1 is hydrogen, X is either C or N, R2 is hydrogen, amine, alkoxy, and/or haloalkyl; Z is either absent or present and when present is methylene; and R4 is either absent or present and when present is optionally substituted aryl (optionally substituted by carboxylic acid).

Preferred compounds having the generic formula IB2, are shown as follows:

4-{5-[2-Menthoxy-acetylamino]-2-methoxy-phenoxymethyl}-benzoic acid;

4-{4-[2-Menthoxy-acetylamino]-phenoxymethyl}-benzoic acid;

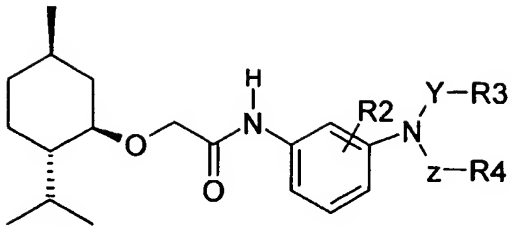
4-{2-Amino-5-[2-menthoxy-acetylamino]-phenoxy}-benzoic acid;

4-{5-[2-Menthoxy-acetylamino]-2-nitro-phenoxy}-benzoic acid;

4-{4-[2-Menthoxy-acetylamino]-3-trifluoromethyl-phenoxymethyl}-benzoic acid;

4-{4-[2-Menthoxy-acetylamino]-3-trifluoromethyl-phenoxymethyl}-benzoic acid;

Another preferred subclass of Formula IB is that group of compounds wherein X is C; D is N; R1 is H; and the amino group is substituted at the meta position of the phenyl ring. This preferred subclass can generally be represented by Formula IB3, as follows:



Formula IB3

wherein R2 is selected from the group consisting of hydrogen, nitro, monoalkylcarbonylalkoxy, optionally substituted arylamido (optionally substituted by hydrogen or haloalkyl), and aralkylamido;

Y is either absent or present and when present is methylene;

R3 is either absent or present and when present is optionally substituted aryl (optionally substituted by hydrogen, hydroxy, and nitro);

Z is either absent or present and when present is selected from the group consisting of methylene and amido;

R4 is either absent or present and when present is selected from the group consisting of optionally substituted aryl (optionally substituted by hydroxy, nitro, tetrazole, optionally substituted aryloxy (optionally substituted by tetrazole), optionally substituted pyridinyloxy (optionally substituted by carboxylic acid, cyano, and tetrazolyl), and optionally substituted pyrrolidine (optionally substituted by hydrogen and carboxylic acid)), optionally substituted piperidinyl (optionally substituted by carboxylic acid), optionally substituted cyclohexane (optionally substituted by carboxylic acid) and carboxylic acid.

Preferred compounds having the generic formula IB3 are as shown as follows:

N-{3-[Bis-(2-hydroxy-5-nitro-benzyl)-amino]-phenyl}-2-menthoxy-acetamide;

3-Hydroxy-4-(3-{3-[2-menthoxy-acetylamino]-phenyl}-ureido)-benzoic acid;

2-Menthoxy-N-{3-[4-(1H-tetrazol-5-yl)-benzylamino]-phenyl}-acetamide;

N-(3-{2,6-Bis-[2-(2H-tetrazol-5-yl)-phenoxy]-benzylamino}-phenyl)-2-menthoxy-acetamide;

N-(3-{2-Fluoro-6-[2-(2H-tetrazol-5-yl)-phenoxy]-benzylamino}-phenyl)-2-(menthoxy)-acetamide;

6-[2-({3-[2-Menthoxy-acetylamino]-phenylamino}-methyl)-6-methoxy-phenoxy]-nicotinic acid;

6-[3-({3-[2-Menthoxy-acetylamino]-phenylamino}-methyl)-phenoxy]-nicotinic acid;

2-Menthoxy-N-(3-{3-methoxy-2-[4-(1H-tetrazol-5-yl)-phenoxy]-benzylamino}-phenyl)-acetamide;

6-{2-[((2-Hydroxy-5-nitro-benzyl)-{3-[2-menthoxy-acetylamino]-phenyl}-amino)-methyl]-6-methoxy-phenoxy}-nicotinic acid;

2-Menthoxy-N-(3-{3-methoxy-2-[5-(1H-tetrazol-5-yl)-pyridin-2-yloxy]-benzylamino}-phenyl)-acetamide;

N-{3-[[2-(5-Cyano-pyridin-2-yloxy)-3-methoxy-benzyl]-(2-hydroxy-5-nitro-benzyl)-amino]-phenyl}-2-(menthoxy)-acetamide;

1 -{3-[2-Menthoxy-acetylamino]-4-nitro-phenyl}-pyrrolidine-2-carboxylic acid;

1-{3-[2-Menthoxy-acetylamino]-4-nitro-phenyl}-piperidine-4-carboxylic acid;

1-{3-[2-Menthoxy-acetylamino]-4-nitro-phenyl}-piperidine-3-carboxylate;

4-{3-[2-Menthoxy-acetylamino]-4-nitro-phenylamino}-cyclohexanecarboxylic acid;

4-{3-[2-Menthoxy-acetylamino]-4-nitro-phenylamino}-cyclohexanecarboxylic acid;

1-{3,4-Bis-[2-menthoxy-acetylamino]-phenyl}-piperidine-4-carboxylic acid;

1-{3-[2-Menthoxy-acetylamino]-4-nitro-phenyl}-azetidine-3-carboxylic acid;

1-[3-[2-Menthoxy-acetylamino]-4-(4-trifluoromethyl-benzoylamino)-phenyl]-piperidine-4-carboxylic acid;

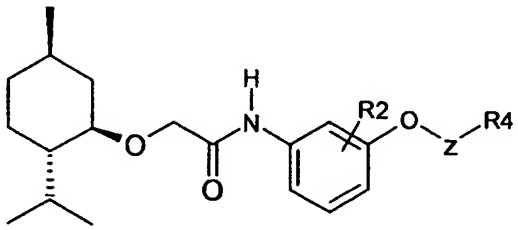
1-{3-[2-Menthoxy-acetylamino]-4-[(naphthalene-1-carbonyl)-amino]-phenyl}-piperidine-4-carboxylic acid;

1-{3-[2-Menthoxy-acetylamino]-4-phenylacetylamino-phenyl}-piperidine-4-carboxylic acid;

1 -{3-[2-Menthoxy-acetylamino]-4-nitro-phenyl}-piperidine-2-carboxylic acid;

6-[2-({3-[2-Menthoxy-acetylamino]-phenylamino}-methyl)-6-methoxy-phenoxy]-nicotinic acid.

A still further preferred subclass of Formula IB is that group of compounds wherein R1 is H, X is C, D is O and is substituted at the meta position of the phenyl ring, and Z is absent. This preferred subclass can generally be represented by Formula IB4, as follows:



Formula IB4

wherein R2 is one or more of hydrogen, alkylamido, alkylamido carboxylic acid, alkyl ester amido, nitro, menthoxyacetylamino, and akloxyarylamido;

Z is absent or present and when present is methylene; and

R4 is optionally substituted phenyl (optionally substituted by carboxylic acid, hydroxy, nitro, alkoxy, tetrazole, and alkyl ester), optionally substituted pyridinyl (optionally substituted by carboxylic acid).

Particularly preferred compounds having the generic formula IB4 are shown as follows:

4-{3-[2-Menthoxy-acetylamino]-phenoxymethyl}-benzoic acid;

N-[3-(2-Hydroxy-5-nitro-benzyloxy)-phenyl]-2-menthoxy-acetamide;

4-{3-[2-Menthoxy-acetylamino]-phenoxymethyl}-3-methoxy-benzoic acid;

2-Menthoxy-N-{3-[4-(1H-tetrazol-5-yl)-benzyloxy]-phenyl}-acetamide;

4-{4-(3-Carboxy-propionylamino)-3-[2-menthoxy-acetylamino]-phenoxy}-benzoic acid methyl ester;

4-{4-Isobutyrylamino-3-[2-menthoxy-acetylamino]-phenoxy}-benzoic acid;

4-{3-[2-Menthoxy-acetylamino]-4-nitro-phenoxy}-benzoic acid;

4-{4-Ethoxycarbonylamino-3-[2-menthoxy-acetylamino]-phenoxy}-benzoic acid;

3-{3-[2-Menthoxy-acetylamino]-4-nitro-phenoxy}-benzoic acid;

6-{3-[2-Menthoxy-acetylamino]-4-nitro-phenoxy}-nicotinic acid;

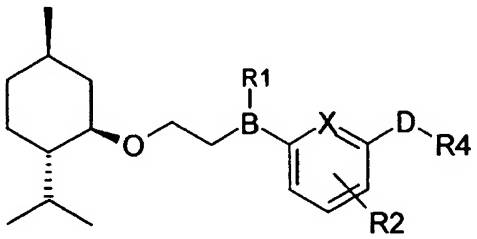
6-{3-[2-Menthoxy-acetylamino]-phenoxy}-nicotinic acid;

4-{3,4-Bis-[2-menthoxy-acetylamino]-phenoxymethyl}-benzoic acid;

4-{3-[2-Menthoxy-acetylamino]-2-nitro-phenoxy}-benzoic acid;

4-{4-(4-Hexyloxy-benzoylamino)-3-[2-menthoxy-acetylamino]-phenoxy}-benzoic acid.

Another preferred subgroup of Formula I is that group of compounds wherein a is 2; b and c are 0; and Y, R3 and Z are absent. The preferred subgroup is represented by Formula IC, as follows:



Formula IC

wherein B is N or O;

R1 is absent when B is O, and is hydrogen when B is N;

X is either C or N;

R2 is selected from the group consisting of hydrogen and nitro;

D is O or N; and

R4 is selected from the group consisting of optionally substituted aryl (optionally substituted with carboxylic acid, morpholinyl alkyl, and optionally substituted arylester (optionally substituted by alkoxy and/or carboxylic acid)), optionally substituted piperidinyl (optionally substituted by carboxylic acid), optionally substituted pyridinyl (optionally substituted by alkenyl), and carboxylic acid substituted cyclohexane;

or R3 and R4 form a carboxylic acid substituted fully saturated monocyclic aza ring with up to 6 carbon atoms.

Particularly preferred compounds of Formula IC are as follows:

4-{5-[2-Menthoxy-ethoxy]-2-nitro-phenoxy}-benzoic acid;

1-{6-[2-Menthoxy-ethylamino]-5-nitro-pyridin-2-yl}-pyrrolidine-2-carboxylic acid;

1-[6-[2-Menthoxy-ethylamino]-5-nitro-pyridin-2-yl]-piperidine-4-carboxylic acid;

4-{6-[2-Menthoxy-ethylamino]-5-nitro-pyridin-2-yloxy}-3-morpholin-4-ylmethyl-benzoic acid;

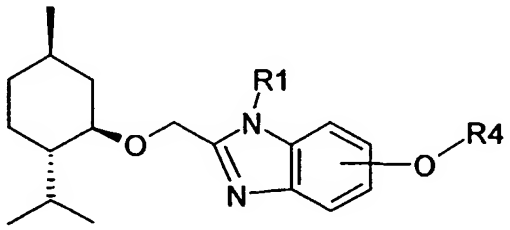
4-{6-[2-Menthoxy-ethylamino]-5-nitro-pyridin-2-yloxy}-benzoic acid;

1-[6-[2-Menthoxy-ethylamino]-5-nitro-pyridin-2-yl]-piperidine-3-carboxylic acid;

6-{6-[2-Menthoxy-ethylamino]-5-nitro-pyridin-2-yloxy}-nicotinic acid;

4-{6-[2-Menthoxy-ethylamino]-5-nitro-pyridin-2-ylamino}-cyclohexane carboxylic acid.

Another preferred subgroup of Formula I is that group of compounds wherein a is 1, b and c are 0, B is N, and A forms benzimidazole with B and the phenyl group. In addition, D is O; and R2 is hydrogen. This subgroup of compounds is generally represented as Formula ID, as shown below:



Formula ID

Preferably, R1 is selected from the group consisting of hydrogen, haloaralkyl and menthoxy-alkyl; and R4 is carboxylic substituted phenyl. Preferred compounds of Formula ID are as follows:

4-[2-(Menthoxy-methyl)-1-(4-trifluoromethyl-benzyl)-1H-benzimidazol-5-yloxy]-benzoic acid;

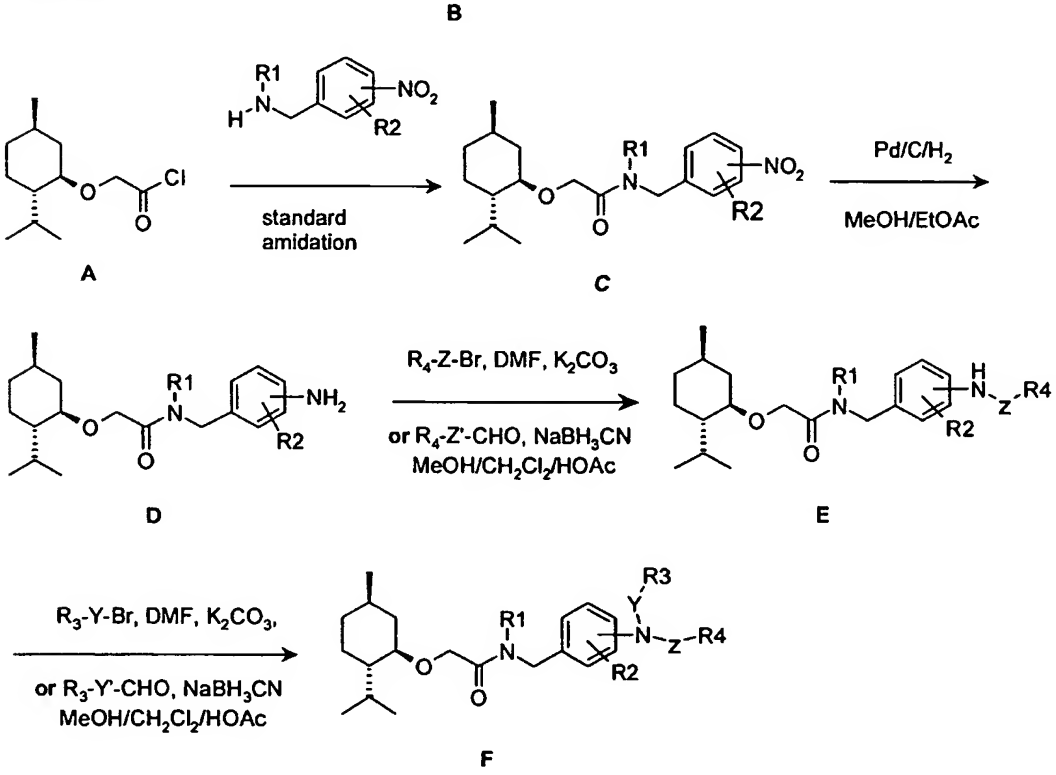
4-[2-Menthoxy-1H-benzoimidazol-5-yloxy]-benzoic acid

4-[1-(2-Menthoxy-ethyl)-2-(menthoxy-methyl)-3H-benzimidazol-5-yloxy]-benzoic acid.

F. Preparation of Compounds

Preparation of Compounds of Formula IA1 and IA2

Scheme 1

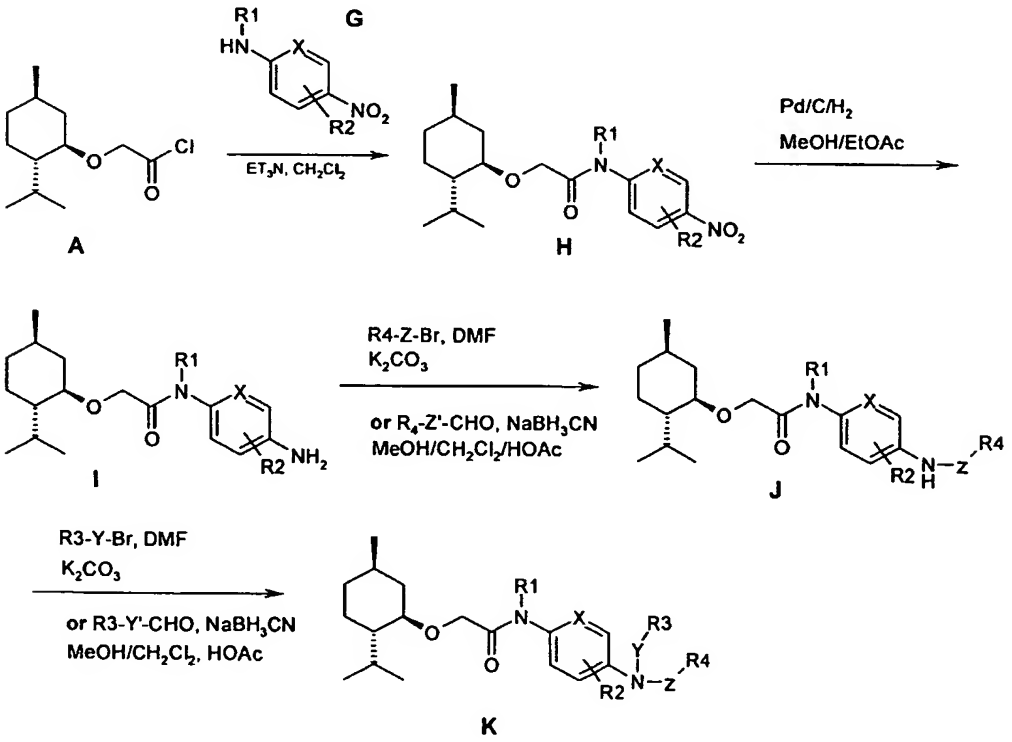


Compounds of formula **E** and **F**, where R_1, R2, R3, R4, Y and Z are as defined above, were prepared as depicted in Scheme 1. Compounds of formula **A** and **B** can be prepared according to methods known to those of ordinary skill in the art or are commercially available, for example, from Aldrich Chemical Company, Inc. or from Maybridge Co.

In general, menthoxy-acetyl chloride **A** (from Aldrich) was subjected to standard amidation, in the presence of base, *e. g.*, triethylamine, with an equimolar amount of substituted phenylmethyl amine **B**, at 0 °C to 40 °C, preferably at ambient temperature, followed by hydrogenation to obtain **D**. Preparation of **E** was achieved either by its direct alkylation with equimolar alkyl bromide (R_4-Z-Br), in the presence of a base, e. g., potassium carbonate, or by its reductive-amination (R_4-Z'-CHO, wherein Z is Z'-CH_2-) using a borohydride as reducing reagents, for example, $NaBH_3CN$, with equimolar aldehydes. Compounds **F** were obtained by dialkylation of **D** (R_4-Z-Br, or R_3-Y-Br), or further alkylation (R_3-Y-Br) and/or reductive-amination (R_3-Y'-CHO, wherein Y is Y'-CH_2-) of **E**.

Preparation of Compounds of Formula IB1

Scheme 2

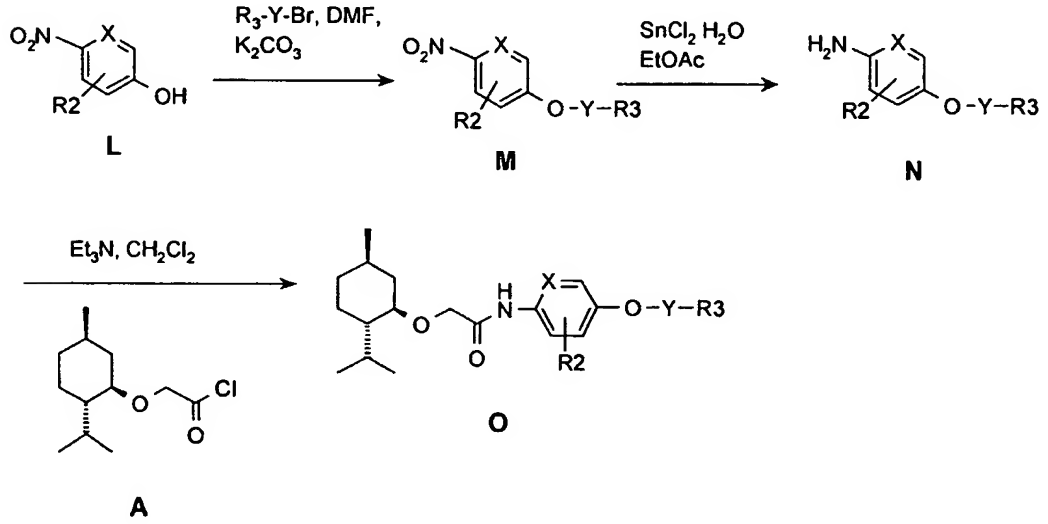


Compounds of formula **J** and **K**, where X, Y, Z, R1, R2, R3 and R4 are as defined above for formula IB1, were prepared as depicted in Scheme 2. Compounds of formula **A** and **G** can be prepared according to methods known to those of ordinary skill in the art or are commercially available, for example, from Aldrich Chemical Company, Inc. or from Maybridge Co.

In general, menthoxy-acetyl chloride **A** (from Aldrich) was subjected to standard amidation, in the presence of base, *e. g.*, triethylamine, with an equimolar amount of substituted aniline **G**, at 0 °C to 40 °C, preferably at ambient temperature, followed by hydrogenation to obtain **H**. Preparation of **J** was achieved either by its direct alkylation of **I** with equimolar alkyl bromide (R_4-Z-Br), in the presence of a base, e. g., potassium carbonate, or by its reductive-amination (R_4-Z'-CHO, wherein Z is Z'-CH_2-) using a borohydride as reducing reagents, for example, $NaBH_3CN$, with equimolar aldehydes. Compounds **K** were obtained by dialkylation of **I** (R_4-Z-Br, or R_3-Y-Br), or further alkylation (R_4-Z-Br) and/or reductive-amination (R_3-Y'-CHO, wherein Y is Y'-CH_2-) of **J**.

Preparation of Compounds of Formula IB2

Scheme 3



Compounds of formula **O**, where R2, R3, Y and X are as defined for formula IB2, were prepared as depicted in Scheme 3. Compounds of formula **L** and alkylbromide (R_3-Y-Br) may be prepared according to methods known to those of ordinary skill in the art or are commercially available, for example, from Aldrich Chemical Company, Inc. or from Maybridge Co.

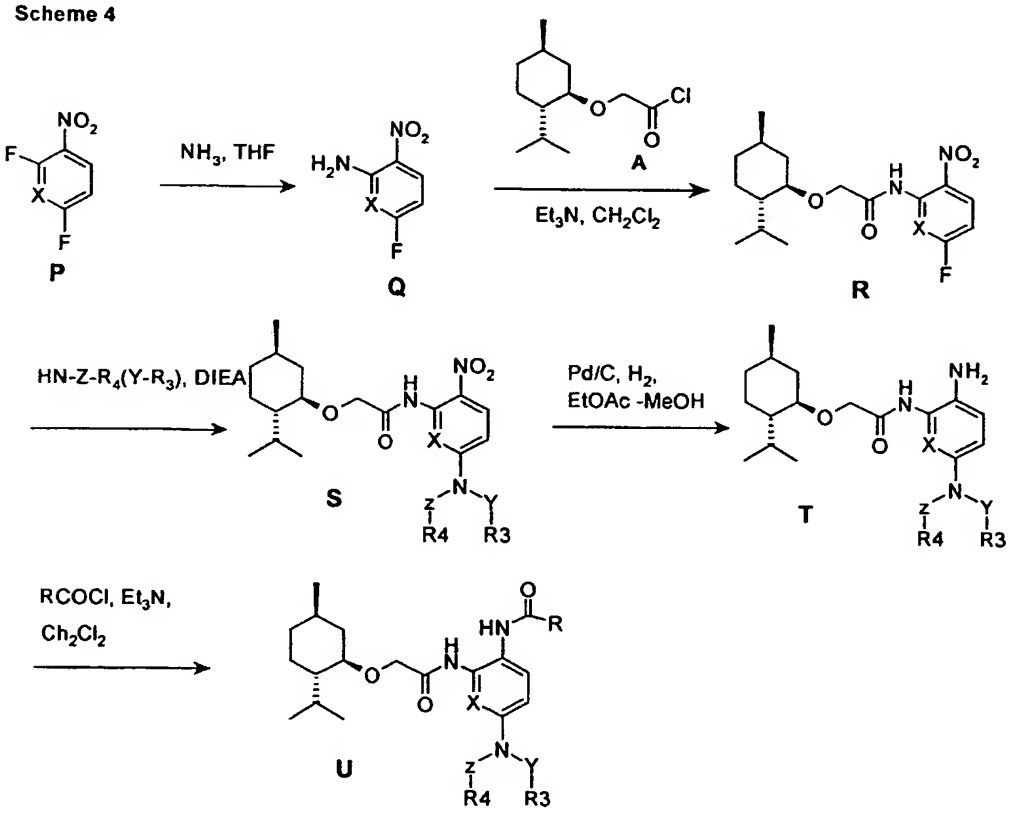
In general, substituted 4-nitrophenol **L** was subjected to standard alkylation, in the presence of base, *e. g.*, potassium carbonate, with an equimolar amount of alkyl bromide (R_3-Y-Br) at 0 °C to 80 °C, preferably at ambient temperature to obtain **M**. Reduction of **M** was achieved by tin chloride to afford **N**. Menthoxy-acetyl chloride **A** (from Aldrich) was subjected

to standard amidation, in the presence of base, *e. g.*, triethylamine, with an equimolar amount of the substituted aniline **N**, at 0 °C to 40 °C, preferably at ambient temperature, to give product **O**.

Preparation of Compounds of Formula IB3

The following Scheme 4 illustrates a general reaction process for making compounds of Formula IB3, specifically, compounds of IB3 wherein the phenyl is substituted with nitro, amine, or carbonylamine, as follows:

Scheme 4



Compounds of formula **S**, **T**, and **U**, where X, R3 and R4 are as defined for formula 1B3, were prepared as depicted in Scheme 4. Compounds of formula **P** can be prepared according to methods known to those of ordinary skill in the art or are commercially available, for example, from Aldrich Chemical Company, Inc. or from Maybridge Co.

In general, substituted difluoronitrobenzene **P** was subjected to addition of ammonia, at -78°C to rt, followed by standard amidation with equimolar menthoxy-acetyl chloride **A** (from

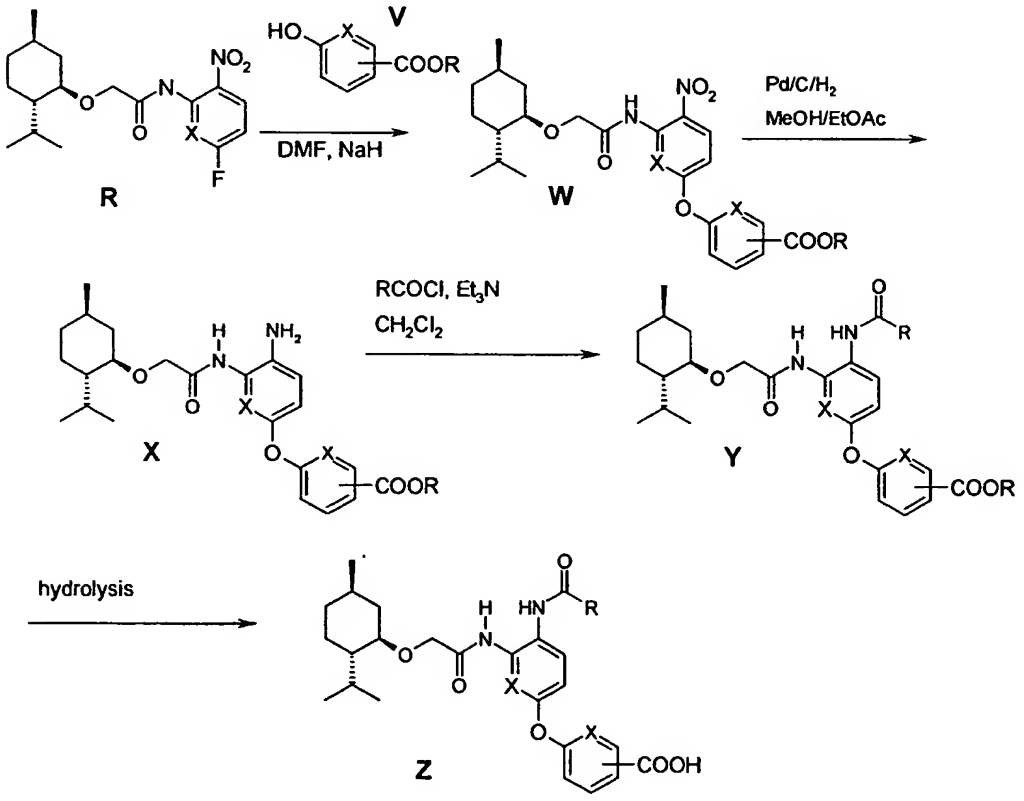
Aldrich), in the presence of base, *e. g.*, triethylamine, at 0 °C to 40 °C, preferably at ambient temperature, to obtain **Q**.

Replacement of fluoride with commercially available amine (HN-Z-R_3(Y-R_4)) at ambient temperature, in the presence of base, *e. g.*, diisopropylethyl amine, to obtain **S**. Hydrogenation of **S** yielded **T**, which reacted further with acetyl chloride, carbamate, and isocyanate to afford **U**.

Preparation of Compounds of Formula IB4

Compounds of Formula IB4 may be made as specified above with respect to Scheme 3. The following Scheme 5 illustrates a general process to make compounds of Formula IB4, specifically where the phenyl group is substituted by nitro, amine or carbonylamine, and wherein R4 is carboxylic acid substituted phenyl or pyridine, as follows:

Scheme 5



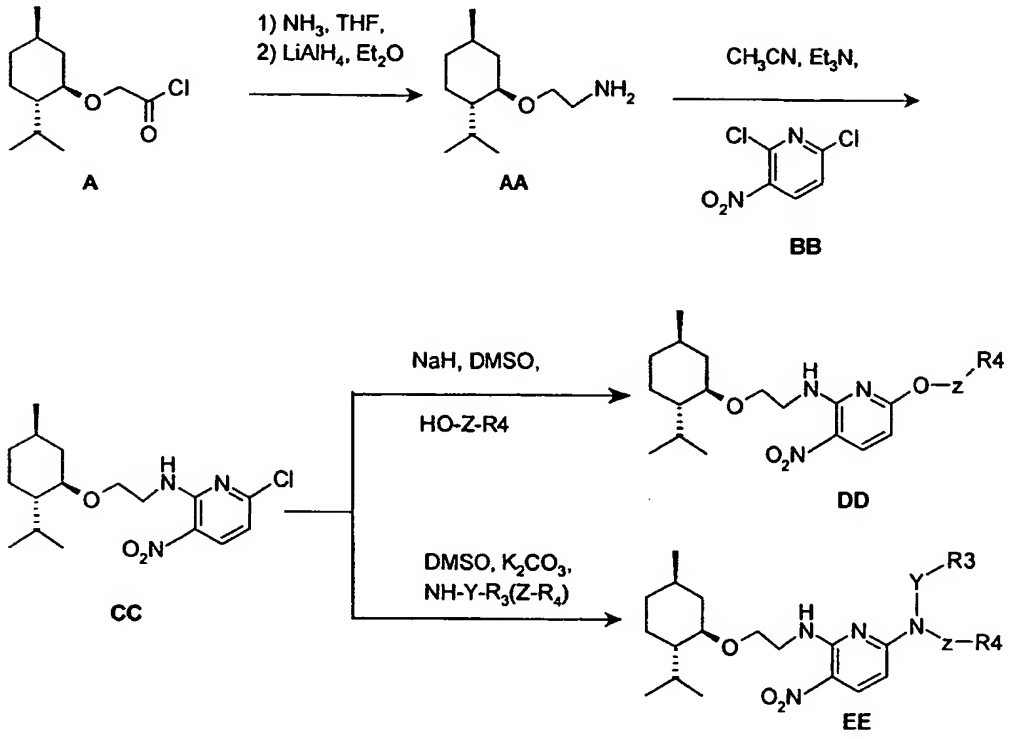
Compounds of formula **X, Y** and **Z** were prepared as depicted in Scheme 5. Hydroxybenzonate, substituted hydroxybenzoic acid, or hydroxypyridinyl acid and ester, are

commercially available, for example, from Aldrich Chemical Company, Inc. or from Maybridge Co.

In general, equimolar commercially available hydroxybenzonate, substituted hydroxybenzoic acid, or hydroxypyridyl acid or ester **V** was added to compound **R** prepared in Scheme 5, in the presence of base, *e. g.*, sodium hydride, at 0 °C to 40 °C, preferably at ambient temperature, to give **W**. Hydrogenation of **W** afforded **X**, which reacted with acetyl chloride, chloroformate, and/or isocyanate to afford **Y**. Hydrolysis under standard conditions afforded **Z**.

Preparation of Compounds of Formula IC

Scheme 6



The following Scheme 6 illustrates a method of making Compounds of Formula IC:

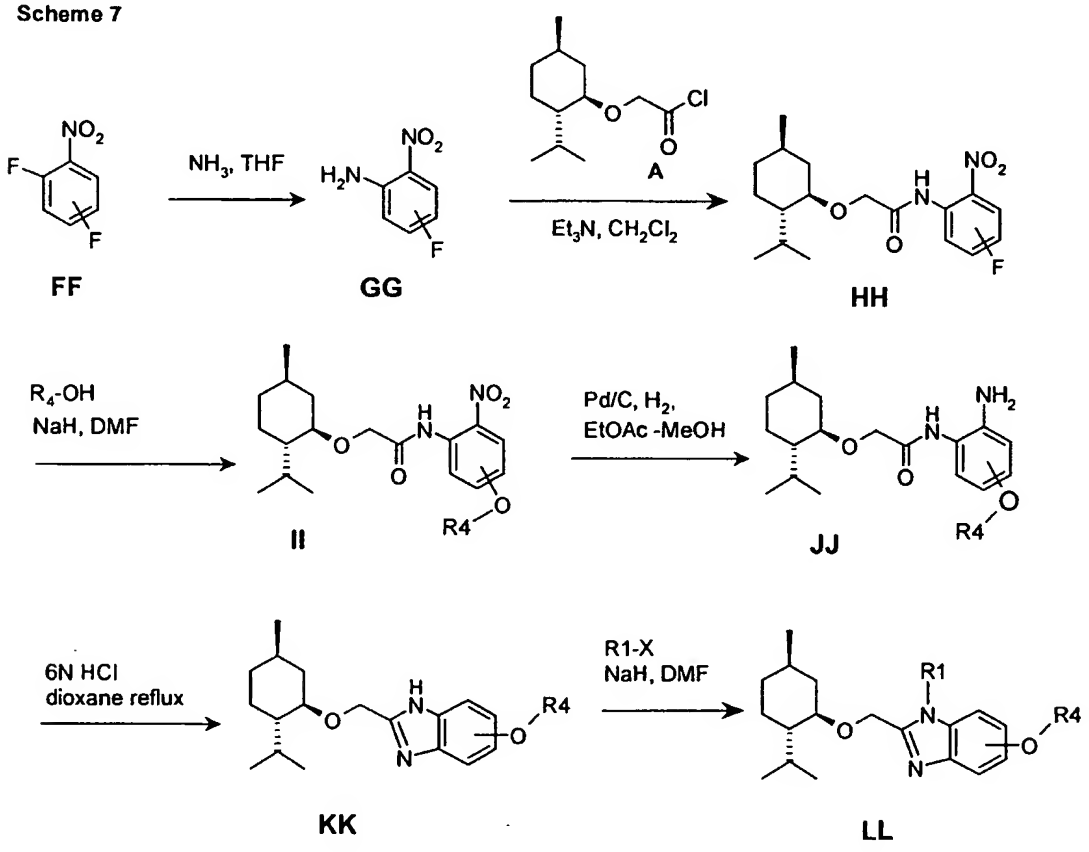
Compounds of formula **DD** and **EE**, where X, R3 and R4 are as defined for formula IC, were prepared as depicted in Scheme 6.

In general, menthoxy-acetyl chloride **A** (from Aldrich) was subjected to standard amidation with large excess of ammonia hydroxide, at 0 °C to 40 °C, preferably at ambient temperature, followed by reduction with $LiAlH_4$ to obtain **AA**. Addition of **AA** to equimolar **BB** (from Aldrich), in the presence of a base, e. g., triethyl amine, to give product **CC**. Addition of commercially available hydroxyalkyl (HO-Z-R4) or amine (NH-Y-R3(Z-R4) afforded products **DD** and **EE**.

Preparation of Compounds of Formula ID:

The following Scheme 6 illustrates a method of making Compounds of Formula ID:

Scheme 7



Compounds of the formula LL, where R1 and R4 are defined for formula ID, above, were prepared as depicted in Scheme 7. Compounds of the Formula FF can be prepared according to methods known to those of ordinary skill in the art.

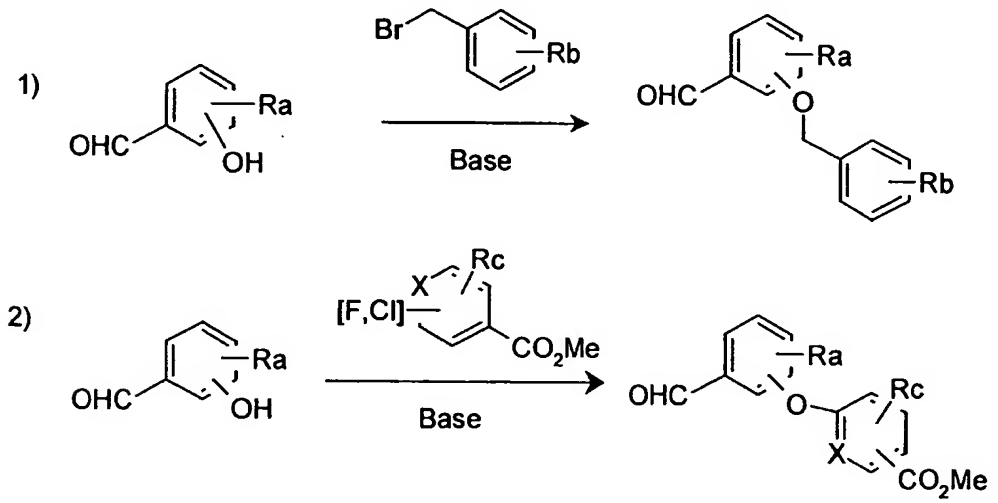
In general, compound HH was prepare in a similar synthetic route as in Scheme 4. Replacement of fluorine with an alkoxy group (R4-O-) in the present of base, e.g., sodium hydride, with an equimolar amount of HH at 0°C to 55°C, preferably at room temperature,

followed by hydrogenation to obtain JJ. Cyclization of JJ in reflux condition, followed by further alkylation with R1-X affords desired product LL in high yields.

Preparation of Intermediates--Substituted Benzaldehydes

The following Scheme 8 illustrates methods of making intermediates that are used throughout the present invention. Specifically, Scheme 8 illustrates methods of making substituted benzaldehydes, as follows:

Scheme 8



Intermediates (e.g., substituted benzaldehydes), may be prepared by the two different methods illustrated in Scheme 8. First, alkylation of substituted phenylmethyl bromide with equimolar substituted hydroxybenzaldehyde in the presence of base, for example, K_2CO_3, afforded substituted benzyl-ether aldehyde.

Second, addition of substituted hydroxybenzaldehyde to halo substituted benzoate, or halo substituted pyridylcarboxylate, in the presence of base, for example, sodium hydride, to give substituted phenyl ether aldehyde.

Examples

The following examples illustrate particularly preferred compounds of the present invention, methods of making the particularly preferred compounds of the present invention, assay methods, and methods of making representative pharmaceutical compositions of the compounds of the present invention.

Example 1

Preparation of 2-Hydroxy-3-[(4-{[2-menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-benzoic acid

1) To a stirred mixture of 4-nitrobenzyl amine hydrochloride (20.3 g, 107.4 mmol) and triethyl amine (27.2 g, 268.5 mmol) in CH_2Cl_2 (300 mL) at 0 °C was added dropwise menthoxy-acetyl chloride (25.0 g, 107.4 mmol). The reaction mixture was allowed to warm to room temperature, and was stirred until TLC indicated that the reaction was finished. The crude product was concentrated to dryness, diluted with EtOAc (300 mL), washed successively with sodium bicarbonate (sat. 50 mL), 5% HCl (2x50 mL), and brine (50 mL). The organic layer was dried over Na_2SO_4, and concentrated to afford 2-[(-)-Menthoxy]-N-(4-nitro-benzyl) acetamide (37.6g) as a yellow oil.

2) A solution of compound 2-(Menthoxy)-N-(4-nitro-benzyl) acetamide (37 g) in EtOAc (150 mL) and MeOH (150 mL) containing 10% Pd/C (2 g) was put under 50 psi hydrogen atmosphere for 2 h. Pd/C was filtered off and the filtrate was concentrated to afford N-(4-amino-benzyl)-2-(methoxy)-acetamide (35 g).

3) A mixture of compound N-(4-amino-benzyl)-2-(menthoxy)-acetamide (124.2 mg, 0.39 mmol) and 2-hydroxy-3-carboxybenzaldehyde (71.2 mg, 0.43 mmol) in MeOH (2 mL), CH_2Cl_2 (2 mL), and HOAc (0.2 mL) was stirred for 1 h at rt, then $NaBH_3CN$ (63 mg, 1 mmol) was added in one portion. After 3 h at rt, the solvent was removed under vacuum, and the resulting residue was diluted with EtOAc (15 mL) and washed with brine (2x5 mL). The organic layer was dried over Na_2SO_4, and concentrated to afford crude product, which was purified further by HPLC using 20 to 80% acetonitrile–water as eluting solvent to give product 2-Hydroxy-3-[(4-{[2-(menthoxy)-acetylamino]-methyl}-phenylamino)-methyl]-benzoic acid as a white solid (164 mg, 90%).

4) ^1H NMR(300 MHz, DMSO): 7.73 (br, 1), 7.61 (d, 1), 7.52 (d, 1), 6.93 (d, 2), 6.84 (t, 1), 6.56 (d, 2), 4.24 (s, 2), 4.17 (m, 2), 3.84 (dd, 2), 3.13 (m, 1), 0.9 ~2.2 (m, 9) 0.81 (d, 6), 0.64 (d, 3)

5) Other compounds made using similar methods as described in Example 1 are as follows:
3-[4-({Allyl-[2-menthoxy-acetyl]-amino}-methyl)-phenylsulfamoyl]-benzoic acid;
N-[4-(2-Hydroxy-5-nitro-benzylamino)-benzyl]-2-menthoxy-acetamide;
4-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-benzoic acid;
4-[3-(4-{[2-Menthoxy-acetylamino]-methyl}-phenyl)ureido]-benzoic acid ethyl ester;

{2-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-4-nitro-phenoxy}-acetic acid;

2-Menthoxy-N-[4-(2,4,5-trihydroxy-benzylamino)-benzyl]-acetamide;

{3-Amino-4-[(4-{[2-menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-phenoxy}-acetic acid;

{4-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-phenyl}-acetic acid;

N-[4-(4,5-Dihydroxy-2-nitro-benzylamino)-benzyl]-2-(menthoxy)-acetamide;

{3-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-phenoxy}-acetic acid;

N-[4-(2-Hydroxy-3,5-dinitro-benzylamino)-benzyl]-2-menthoxy-acetamide;

N-[4-(2-Hydroxy-5-nitro-benzylamino)-benzyl]-2-menthoxy-acetamide;

N-{4-[(2-Hydroxy-5-nitro-phenylamino)-methyl]-benzyl}-2-menthoxy-acetamide;

[4-(2-Hydroxy-5-nitro-benzylamino)-benzyl]-carbamic acid-menthoxy ester;

4-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-benzo[1,3]dioxole-2,2-dicarboxylic acid methyl ester;

Example 2

Preparation of N-{4-[(2-Hydroxy-5-nitro-benzyl)-methyl-amino]-benzyl}-2-menthoxy-acetamide

1) To a stirred solution of N-(4-amino-benzyl)-2-menthoxy-acetamide (644.3 mg, 2 mmol) in DMF (10 mL), was added K_2CO_3 (280 mg, 2 mmol) and CH_3I (274 mg, 2 mmol). After 4 h at rt, the reaction was diluted with dichloromethane (15 mL), and water (10 mL), extracted with dichloromethane (2x10 mL), and washed with brine (2X5 mL). The organic layer was dried over Na_2SO_4 and concentrated to give crude product for the next step of the reaction.

2) After the mixture of starting material (546.3 mg, 1.6 mmol) obtained in step 1 and 2-hydroxy-5-nitrobenzaldehyde (270 mg, 1.6 mmol) in $ClCH_2CH_2Cl$ (5 mL) was stirred for 15 min, $NaBH(OAc)_3$ (490 mg, 2.3 mmol) was added. The reaction mixture was stirred for additional 4 h, then poured into cooled water (15 mL), extracted with EtOAc (3x15 mL), and washed with brine (2x5 mL). The organic layer was dried over Na_2SO_4, and concentrated to afford crude product, which was purified by flash chromatography to afford N-{4-[(2-Hydroxy-5-nitro-benzyl)-methyl-amino]-benzyl}-2-menthoxy-acetamide (617 mg, 86%).

3) ^1H NMR (300 MHz, $CDCl_3$): 8.14 (d, 1), 7.95 (s, 1), 7.32 (d, 2), 7.04 (d, 2), 6.92 (d, 1), 4.43 (m, 4), 4.16 (m, 2), 3.21 (m, 1), 2.89 (s, 3), 0.8~2.05 (m, 9), 0.89 (d, 6), 0.71 (d, 3)

4) Other compounds made using similar methods as described above in Example 2 are as follows:

N-{4-[Bis-(2-hydroxy-5-nitro-benzyl)-amino]-benzyl}-2-menthoxy-acetamide;

2-(Menthoxy)-N-(4-{(2-hydroxy-5-nitro-benzyl)-[2-(2-hydroxy-5-nitro-benzyloxy)-5-nitro-benzyl]-amino}-benzyl)-acetamide;

N-{4-[Bis-(2-hydroxy-5-nitro-benzyl)-amino]-benzyl}-2-menthoxy-acetamide;

[(2-Hydroxy-3-hydroxymethyl-5-nitro-benzyl)-(4-{[2-menthoxy-acetylamino]-methyl}-phenyl)-amino]-acetic acid;

N-(4-{[2-(2-Hydroxy-5-nitro-benzyloxy)-5-nitro-benzyl]-methyl-amino}-benzyl)-2-menthoxy-acetamide;

2-(2-{[(2-Hydroxy-3-methoxy-benzyl)-(4-{[2-menthoxy-acetylamino]-methyl}-phenyl)-amino]-methyl}-6-methoxy-phenoxy)-5-nitro-benzoic acid;

N-(4-{[2-(2-Hydroxy-5-nitro-benzyloxy)-5-nitro-benzyl]-methyl-amino}-benzyl)-2-menthoxy-acetamide;

4-(2-{[(4-{[2-Menthoxy-acetylamino]-methyl}-phenyl)-methyl-amino]-methyl}-4-nitro-phenoxymethyl)-benzoic acid;

Example 3

Preparation of 2-{2-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-6-methoxy-phenoxy}-5-nitro-benzoic acid

1) To a stirred solution of 2-hydroxy-3-methoxybenzaldehyde (18.2 g, 119.5 mmol) in DMSO (400 mL) was added potassium *tert*-butoxide (14.8 g, 131.5 mmol) at rt. After 1 h, 2-chloro-5-nitromethylbenzonate (25.8 g, 119.5 mmol) was added, then kept at 110 °C for 4 h. The reaction mixture was cooled to rt, and poured into ice-water (300 mL). The white solid precipitated, filtered to collect solid, and re-crystallization by EtOAc to give product (33g, 83.3%) as white crystals.

2) The mixture of the above aldehyde (1 g, 3.1 mmol) and N-(4-amino-benzyl)-2-menthoxy-acetamide (1 g, 3.1 mmol) were mixed in CH_2Cl_2 (10 m), MeOH (10 mL), and HOAc (2 mL) for 1h, at which time $NaBH_3CN$ (590 mg, 9.42 mmol) was added, and the reaction was stirred for additional 1.5h. The reaction mixture was concentrated to dryness, and diluted with EtOAc (100 mL) and water (30 mL). The organic layer was dried over Na_2SO_4 and concentrated to give crude product (1.5 g). To a stirred solution of this product (550 mg, 0.84 mmol) in THF

(5 mL) and MeOH (5 mL) was added $LiOH \bullet H_2O$(100 mg, 2.4 mmol) dissolved in water (5 mL). The reaction was stirred at rt for 4 h, and then quenched with 1 N HCl to pH 3~4, extracted with EtOAc (3x20 mL), washed with brine (2x10 m). The organic layer was dried over Na_2SO_4 and concentrated to give crude product, which was purified by prep-HPLC to give 2-{2-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-6-methoxy-phenoxy}-5-nitro-benzoic acid (440 mg, 82.1%).

3) ^1H NMR (300 MHz, DMSO): 8.61 (s, 1), 8.3 (d, 1), 7.76 (m, 1), 7.24 (m, 1), 7.16 (m, 1), 6.97 (d, 2), 6.63 (m, 1), 6.52 (d, 2), 3.64 ~4.25 (m, 6), 3.13 (m, 1), 2.16 (m, 1), 1.96 (m, 1), 1.54 (m, 2), 1.27 (m, 2), 0.64~0.95 (m, 8), 0.61 (d, 3).

4) Other compounds made using similar methods as described in Example 3 are as follows (^1H NMR data included for particularly preferred compounds):

3-Hydroxy-4-{4-[2-menthoxy-acetylamino]-piperidin-1-ylmethyl}-8-methoxy-1,9-dimethyl-11-oxo-11H-dibenzo[b,e][1,4]dioxepine-6-carboxylic acid [(300 MHz, DMSO): δ 7.00 (s, 1), 6.98 (d, 2), 6.74 (d, 2), 6.62 (s, 1), 4.75 (s, 1), 4.24 - 4.42 (m, 2), 4.19 (m, 1), 4.04 (m, 1), 3.82 (s, 3), 3.10 (m, 3), 2.32 (s, 3), 2.16 (s, 3), 2.00 - 2.22 (m, 2), 1.00 - 1.70 (m, 9), 0.60 - 1.00 (m, 14)];

2-(2-{[(2-Hydroxy-3-methoxy-benzyl)-(4-{[2-menthoxy-acetylamino]-methyl}-phenyl)-amino]-methyl}-6-methoxy-phenoxy)-5-nitro-benzoic acid;

3-Hydroxy-4-[(4-{[2-menthoxy-acetylamino] methyl}-phenylamino)-methyl]-8-methoxy-1,9-dimethyl-11-oxo-11H-dibenzo[b,e][1,4]dioxepine-6-carboxylic acid;

5-{2-[3-(4-{[2-Menthoxy-acetylamino]-methyl}-phenyl)-ureido]-4-methoxycarbonyl-phenoxy}-isophthalic acid dimethyl ester;

2-{2-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-phenoxy}-5-methoxy-benzoic acid;

2-{2-Carbamoyl-5-hydroxy-6-[(4-{[2-menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-3-methyl-phenoxy}-3-hydroxy-5-methoxy-4-methyl-benzoic acid;

2-{3-Fluoro-2-[(4-{[2-menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-phenoxy}-5-methoxy-benzoic acid;

2-{2-[(4-{[2-Menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-4-nitro-phenoxy}-4-phenoxy-benzoic acid;

3-{3-Fluoro-2-[(4-{[2-menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-phenoxy}-2-hydroxy-benzoic acid;

2-Menthoxy-N-(4-{5-nitro-2-[4-(1H-tetrazol-5-yl)-benzyloxy]-benzylamino}-benzyl)-acetamide;

5-Amino-2-{2-[(4-{[2-menthoxy-acetylamino]-methyl}-phenylamino)-methyl]-6-methoxy-phenoxy}-benzoic acid;

Example 4

Preparation of 1-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-nitro-phenyl]-piperidine-3-carboxylic acid

1) To a stirred mixture of 2-methoxy-4-nitroaniline (841 mg, 5 mmol) and triethyl amine (1.5 mL) in CH_2Cl_2 (20 mL) at rt was added dropwise menthoxy-acetyl chloride (1.16 g, 5 mmol). The reaction mixture was stirred until TLC indicated that the reaction was finished. The crude product was concentrated to dryness, diluted with EtOAc (30 mL), washed successively with sodium bicarbonate (sat. 5 mL), 5% HCl (2x5 mL), and brine (5 mL). The organic layer was dried over Na_2SO_4, and concentrated to afford 2-Menthoxy-N-(2-methoxy-4-nitro-phenyl)-acetamide (1.76) as a yellow oil.

2) A solution of 2-Menthoxy-N-(2-methoxy-4-nitro-phenyl)-acetamide (1.7 g) in EtOAc (10 mL) and MeOH (10 mL) containing 10% Pd/C (0.15 g) was put under 50 psi hydrogen atmosphere for 2 h. Pd/C was filtered off and the filtrate was concentrated to afford N-(4-amino-2-methoxy-phenyl)-2-(menthoxy)-acetamide (1.62 g).

3) A mixture of N-(4-amino-2-methoxy-phenyl)-2-(menthoxy)-acetamide (1.62 g) (334.46 mg, 1.1 mmol) and 2,6-difluoro-3-nitrobenzaldehyde (187.1 mg, 1.0 mmol) in CH_2Cl_2 (5 mL), and HOAc (0.2 mL) was stirred for 1 hour at rt, then $NaBH_3CN$ (63 mg, 1.1 mmol) was added in one portion. After 3 h at rt, the solvent was removed under vacuum, and the resulting residue was diluted with EtOAc (15 mL) and washed with brine (2x5 mL). The organic layer was dried over Na_2SO_4, and concentrated to afford crude product, which was purified further by flash chromatography give product N-[4-(2,6-difluoro-3-nitro-benzylamino)-2-methoxy-phenyl]-2-(menthoxy)-acetamide (470 mg, 93%).

4) The mixture of N-[4-(2,6-difluoro-3-nitro-benzylamino)-2-methoxy-phenyl]-2-(menthoxy)-acetamide (1.6 g, 3.16 mmol), K_2CO_3 (0.48 g, 3.48 mmol), and ethyl (-)-nipecolate (0.5 g, 3.16 mmol) in DMSO was kept at 50°C for 8 h. The reaction mixture was poured into ice-water (60 mL), and extracted with EtOAc (3x40 mL). The organic layer was dried over Na_2SO_4, and concentrated to afford crude product, which was purified further by flash

chromatography to afford product for hydrolysis. To a stirred solution of ester (0.9 g, 1.4 mmol) in THF (25 mL) was added LiOH (235 mg, 5.6 mmol) in water (5 mL) at room temperature. After stirring at rt overnight, the reaction was acidified with 1N HCl to pH 5 ~ 6, then extracted with EtOAc (3x40 mL). The organic layer was dried over Na_2SO_4, and concentrated to afford crude product, which was purified further by HPLC with 20-80% acetonitrile-water as eluting solvents to afford 1-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-nitro-phenyl]-piperidine-3-carboxylic acid as a white solid (900 mg, 94%).

5) ^{1}H NMR(300 MHz, DMSO): 8.58 (s, 1), 8.02 (m, 1), 7.84 (m, 1), 7.01 (d, 1), 6.46 (s, 1), 6.27 (d, 1), 4.22 (s, 2), 4.07 (d, 1), 3.85 (d, 1), 3.78 (s, 3), 3.2~3.6(m, 3), 3.0 (m, 1), 2.81 (m, 1), 2.67 (m,1), 2.23(m, 1), 2.04 (m, 1), 1.92 (m, 1), 1.1~1.83 (m, 10), 0.91 (d, 6), 0.73 (d, 3).

6) Other compounds made using similar methods as described in Example 4 are as follows:

N-[5-(2-Hydroxy-5-nitro-benzylamino)-pyridin-2-yl]-2-menthoxy-acetamide;

2-Menthoxy-N-(4-{(2-hydroxy-5-nitro-benzyl)-[2-(2-hydroxy-5-nitro-benzyloxy)-5-nitro-benzyl]-amino}-phenyl)-acetamide;

3,4,5,6-Tetrafluoro-N-{4-[2-menthoxy-acetylamino]-phenyl}-phthalamic acid;

N-[4-(2-Hydroxy-5-nitro-benzylamino)-2-methoxy-phenyl]-2-menthoxy-acetamide;

N-{4-[Bis-(2-hydroxy-5-nitro-benzyl)-amino]-2-methoxy-phenyl}-2-menthoxy-acetamide;

1-{5-[Bis-(2-hydroxy-5-nitro-benzyl)-amino]-2,3-dihydro-indol-1-yl}-2-menthoxy-ethanone;

N-[1-(2-Hydroxy-5-nitro-benzyl)-2,3-dihydro-1H-indol-5-yl]-2-menthoxy-acetamide;

4-({4-[2-Menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-benzoic acid;

2-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-phenylamino}-methyl)-phenoxy]-benzoic acid;

2-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-phenylamino}-methyl)phenoxy]-3-methoxy-benzoic acid;

4-({4-[2-Menthoxy-acetylamino]-2,5-dimethoxy-phenylamino}-methyl)-benzoic acid;

4-({4-[2-Menthoxy-acetylamino]-5-methoxy-2-methyl-phenylamino}-methyl)-benzoic acid;

4-{2-(3-Carboxy-propionylamino)-5-[2-menthoxy-acetylamino]-phenoxy}-benzoic acid methyl ester;

2-Hydroxy-3-({4-[2-menthoxy-acetylamino]-5-methoxy-2-methylphenylamino}-methyl)-benzoic acid;

2-[2-({4-[2-Menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-methoxy-phenoxy]-nicotinic acid;

6-[2-({4-[2-Menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-methoxy-phenoxy]-nicotinic acid;

1-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-nitro-phenyl]-piperidine-3-carboxylic acid;

5-Bromo-2-[3-fluoro-2-({4-[2-menthoxy-acetylamino]-phenylamino}-methyl)-phenoxy]-benzoic acid;

4-{2-Acetylamino-5-[2-menthoxy-acetylamino]-phenoxy}-benzoic acid;

1-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-nitro-phenyl]-pyrrolidine-2-carboxylic acid methyl ester;

4-{2-Ethoxycarbonylamino-5-[2-menthoxy-acetylamino]-phenoxy}-benzoic acid;

1-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-nitro-phenyl]-pyrrolidine-2-carboxylic acid methyl ester;

1-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-nitro-phenyl]-pyrrolidine-2-carboxylic acid;

4-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-nitro-phenoxy]-benzoic acid;

1-[6-Amino-3-fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-phenyl]-piperidine-4-carboxylic acid;

4-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-4-nitro-phenoxy]-benzoic acid;

1-{4-Ethoxycarbonylamino-2-[(ethoxycarbonyl-{4-[2-menthoxy-acetylamino]-3-methoxy-phenyl}-amino)-methyl]-3-fluoro-phenyl}-piperidine-4-carboxylic acid;

1-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-methanesulfonylamino-phenyl]-piperidine-4-carboxylic acid;

4-[2-({4-[2-Menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-3-methoxy-6-nitro-phenoxy]-3,5-dimethoxy-benzoic acid;

6-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-nitro-phenoxy]-nicotinic acid;

1-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-phenyl]-piperidine-4-carboxylic acid;

4-Chloro-2-[2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-methoxy-phenoxy]-benzoic acid;

4-Acetyl-1-{2-[(acetyl-{4-[2-menthoxy-acetylamino]-3-methoxy-phenyl}-amino)-methyl]-3-fluoro-6-nitro-phenyl}piperazine-2-carboxylic acid;

4-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-nitro-phenyl]-piperazine-1,3-dicarboxylic acid 1-methyl ester;

6-[4-Fluoro-5-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-2-nitro-phenoxy]-pyridine-2-carboxylic acid methyl ester;

1-[3-Fluoro-2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-methoxycarbonylamino-phenyl]-piperidine-4-carboxylic acid;

6-Fluoro-2-[2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-methoxy-phenoxy]-3-nitro-benzoic acid;

4-{2,5-Bis-[2-menthoxy-acetylamino]-phenoxy}-benzoic acid;

5-Chloro-2-[2-({4-[2-menthoxy-acetylamino]-3-methoxy-phenylamino}-methyl)-6-methoxy-phenoxy]-3-nitro-benzoic acid;

4-{5-[2-Menthoxy-acetylamino]-2-methyl-benzoimidazol-1-ylmethyl}-benzoic acid;

N-[4-(2-Hydroxy-5-nitro-benzylamino)-phenyl]-2-menthoxy-acetamide.

Example 5

Preparation of 4-{4-[2-Menthoxy-acetylamino]-3-trifluoromethyl-phenoxymethyl}-benzoic acid

1) The mixture of 4-hydroxy-2-trifluoromethylnitrobenzene (1 g, 6.53 mmol), K_2CO_3 (1.1g, 7.97 mmol), methyl 4-bromobenzonate (1.6 g, 6.99 mmol) in acetonitrile (40 mL) was kept at reflux until TLC indicated reaction completed. The reaction mixture was cooled and filtered through a thin pad of Celite. The filtrate was concentrated and dried. The crude was purified by column chromatography to give 4-(4-nitro-3-trifluoromethyl-phenoxymethyl)-benzoic acid methyl ester as a white solid (1.4 g, 74%)

2) A suspension of nitrobenzene 4-(4-nitro-3-trifluoromethyl-phenoxymethyl)-benzoic acid methyl ester (400 mg, 1.33 mmol) and tin chloride (1.3 g, 5.32 mmol) in EtOAc (50 mL) was stirred at reflux until the starting material was no longer present on TLC. The reaction mixture was cooled and basified with 30% NaOH (20 mL), and was extracted with EtOAc (3x60 mL).The organic layer was dried over Na_2SO_4, and concentrated to give crude 4-(4-amino-3-triflouromethyl-phenoxymethyl)-benzoic acid methyl ester. To a solution of 4-(4-amino-3-triflouromethyl-phenoxymethyl)-benzoic acid methyl ester (400 mg, 1.48 mmol) and

Menthoxyacetyl chloride (412 mg, 1.78 mmol) was added triethyl amine (0.5 mL). The resulting solution was stirred overnight. The crude product was concentrated to dryness, diluted with EtOAc (30 mL), washed successively with sodium bicarbonate (sat. 5 mL), 5% HCl (5 mL), and brine (5 mL). The organic layer was dried over Na_2SO_4, and concentrated to afford crude product. Purification by flash chromatography to afford 4-{4-[2-(Menthoxy)-acetylamino]-3-trifluoromethyl-phenoxymethyl}-benzoic acid methyl ester (679 mg, 92%) as a brown oil.

3) To a stirred solution of 4-{4-[2-(Menthoxy)-acetylamino]-3-trifluoromethyl-phenoxymethyl}-benzoic acid methyl ester (310 mg, 0.66 mmol) in THF (4 mL) and MeOH (4 mL) was added LiOH (200 mg, 8.3 mmol) in H_2O (5 mL) at room temperature. The reaction was completed after 6 h at rt, and diluted with water (10 mL), acidified with 1 N HCl to pH 5~6, and extracted with EtOAc (3x20 mL). The organic layer was dried over Na_2SO_4, and concentrated to afford crude product. Purification by prep-HPLC to afford 4-{4-[2-Menthoxy-acetylamino]-3-trifluoromethyl-phenoxymethyl}-benzoic acid (102 mg, ~33%) as a white solid.

4) ^{1}H NMR (300 MHz, DMSO), 10.01 (s, 1), 8.54 (s, 1), 8.02 (d, 2), 7.63 (d, 2), 6.84 (m, 2), 4. 11 (m, 2), 3.01 ~3.33 (m, 3), 1.04 ~2.27 (m, 6), 0.6~0.9 (m, 10).

5) Other compounds made using similar methods as described in Example 5 are as follows:

4-{5-[2-Menthoxy-acetylamino]-2-methoxy-phenoxymethyl}-benzoic acid;

4-{4-[2-Menthoxy-acetylamino]-phenoxymethyl}-benzoic acid;

4-{2-Amino-5-[2-menthoxyacetylamino]-phenoxy}-benzoic acid;

4-{5-[2-Menthoxy-acetylamino]-2-nitro-phenoxy}-benzoic acid;

4-{4-[2-Menthoxy-acetylamino]-3-trifluoromethyl-phenoxymethyl}-benzoic acid;

4-{4-[2-Menthoxy-acetylamino]-3-trifluoromethyl-phenoxymethyl}-benzoic acid.

Example 6

Preparation of N-{6-[Bis-(2-hydroxy-5-nitro-benzyl)-amino]-4H-benzo[1,3]dioxin-8-ylmethyl}-2-menthoxy-acetamide

1) Liquid ammonia was collected in a sealed tube containing a solution of 5-chloromethyl-7-nitro-2,3-dihydro-benzo[1,3]dioxine (8 g, 34.8 mmol) in THF (200 mL) at –78 °C. The reaction mixture was stirred and allowed to warm to rt overnight, then was stripped down to dryness. The reaction mixture was diluted with EtOAc (100 mL), and brine (30 mL), and extracted with EtOAc (3x25 mL). The organic layer was dried over Na_2SO_4, and was concentrated to give

crude product, which was purified further by flash chromatography to give benzylamine (5.4 g, 77%).

2) To a stirred solution of 7-nitro-2,3-dihydro-benzo[1,3]dioxin-5-yl)-methylamine (4.7 g, 22.3 mmol) in dichloromethane (75 mL) at 0°C, was added triethyl amine (2 mL) and Menthoxyacetyl chloride (5.7 g, 24.5 mmol) successively. After addition, the reaction mixture was allowed to warm to rt, and stirred for additional 10 h. The reaction mixture was concentrated to dryness, and diluted with EtOAc (200 mL), then washed with sodium bicarbonate (sat. 30 mL), and 5% HCl (20 mL) successively. The organic layer was dried over Na_2SO_4, and was concentrated to give crude product, which was purified further by flash chromatography to give 2-(Menthoxy)-N-(7-nitro-2,3-dihydro-benzo[1,3]dioxin-5-ylmethyl)-acetamide (8.6 g, 95%).

3) A solution of 2-(Menthoxy)-N-(7-nitro-2,3-dihydro-benzo[1,3]dioxin-5-ylmethyl)-acetamide (7.1 g) in EtOAc (75 mL) and MeOH (75 mL) containing 10% Pd/C (0.5 g) was put under 50 psi hydrogen atmosphere for 2 hours. Pd/C was filtered off and the filtrate was concentrated to afford N-(7-amino-2,3-dihydro-benzo[1,3]dioxin-5-ylmethyl)-2-(menthoxy)-acetamide (6.7 g).

4) To a solution of N-(7-amino-2,3-dihydro-benzo[1,3]dioxin-5-ylmethyl)-2-(menthoxy)-acetamide (200mg, 0.53 mmol) in DMF(5 mL) was added K_2CO_3 (0.5 g, 3.6 mmol) and 2-hydroxy-5-nitrobenzylbromide (500 mg, 2.15 mmol) at rt. The reaction mixture was stirred at 60 °C overnight, and then cooled to rt, and quenched with brine (20 mL), extracted with EtOAc (3x15 mL). The organic layer was dried over Na_2SO_4, and concentrated to crude product. Purification by prep-HPLC afforded N-{6-[Bis-(2-hydroxy-5-nitro-benzyl)-amino]-4H-benzo[1,3]dioxin-8-ylmethyl}-2-menthoxy-acetamide (90 mg) as a yellow solid.

5) ^{1}H NMR (DSMO-d_6/TFA) 7.95 (d, 2), 7.82 (s, 2), 7.51 (m, 1), 6.97 (d, 2), 6.46 (s, 1), 6.38 (s, 1), 5.16 (s, 2), 4.64 (s, 2), 4.53 (s, 4), 4.11 (m, 2), 3.76 (d, 1), 3.61 (d, 1), 2.98 (m, 1), 2.04 (m, 1), 1.96 (m, 1), 1.41-1.60 (m, 2), 1.11-1.37 (m, 2), 0.65-0.91 (m, 6), 0.59 (d,3).

6) Other compounds made using similar methods as described in Example 6 are as follows (^{1}H NMR data included for particularly preferred compounds):

N-(6-{(2-Hydroxy-5-nitro-benzyl)-[2-(2-hydroxy-5-nitro-benzyloxy)-5-nitro-benzyl]-amino}-4H-benzo[1,3]dioxin-8-ylmethyl)-2-menthoxy-acetamide [(DSMO-d_6/TFA) 7.96 (m, 3), 7.81 (m, 3), 7.51 (m, 2), 6.95 (m, 2), 6.47 (s, 1), 6.38 (s, 1), 5.17 (s, 2), 4.62 (s, 2),

4.57 (s, 4), 4.41 (s, 2), 4.11 (m, 2), 3.96 (s, 2), 3.76 (d, 1), 3.60 (d, 1), 2.98 (m, 1), 2.04 (m, 1), 1.96 (m, 1), 1.30-1.60 (m, 2), 1.11-1.36 (m, 2), 0.65-0.91 (m, 7), 0.59 (d, 3)];

N-[6-(2-Hydroxy-5-nitro-benzylamino)-4H-benzo[1,3]dioxin-8-ylmethyl]-2-menthoxy-acetamide.

Example 7

Preparation of 4-[2-Menthoxy-1H-benzoimidazol-5-yloxy]-benzoic acid

1) Liquid ammonia was collected in a sealed tube containing a solution of 2, 4-difluoronitrobenzene (14.5 g, 91.2 mmol) in THF (100 mL) at –78 °C. The reaction mixture was allowed to warm to rt overnight. The tube was recooled to -78 °C, and vented. The solvent was removed under vacuum, and the resulting residue was dissolved in EtOAc (150 mL) and water (40 mL). The organic layer was washed with water (2x100 mL), dried and concentrated to give orange-yellow crystals (13.5 g, 95%). To a stirred solution of aniline (5.0 g, 32 mmol) in dichloromethane (100 mL) at rt was added triethyl amine (6.5g, 64 mmol) and Menthoxyacetyl chloride (8.94 g, 38.4 mmol) successively. After addition, the reaction mixture was allowed to warm to rt, and stirred for additional 2 days. The reaction mixture was concentrated to dryness, and diluted with EtOAc (250 mL), then washed with sodium bicarbonate (sat. 50 mL), and 5% HCl (50 mL) successively. The organic layer was dried over Na_2SO_4, and was concentrated to give crude product, which was purified further by flash chromatography to give product N-(5-fluoro-2-nitro-phenyl)-2-(menthoxy)-acetamide (5g, 44%).

2) To a stirred solution of 4-hydroxymethylbenzoate (2.7 g, 18 mmol) in DMF (75 mL), was added sodium hydride (726 mg, 18 mmol). After 20 min, the homogeneous solution was added to a solution of product N-(5-fluoro-2-nitro-phenyl)-2-(menthoxy)-acetamide (3.2 g, 9.0 mmol) in DMF (75 mL). After 4 h, TLC shows complete consumption of starting material. EtOAc/water workup, and concentration gave a crude gum. This was chromatographed with 4:1/hexane/ethyl acetate to give the desired product 4-{3-[2-(Menthoxy)-acetylamino]-4-nitro-phenoxy}-benzoic acid methyl ester (4.1 g, 93%) as an oil.

3) A solution of 4-{3-[2-(Menthoxy)-acetylamino]-4-nitro-phenoxy}-benzoic acid methyl ester (4g, 8.2 mmol) in EtOAc (150 mL) containing 10% Pd/C (0.5 g) was put under 50 psi hydrogen atmosphere for 1.5 hours. Pd/C was filtered off and the filtrate was concentrated to afford 4-{4-Amino-3-[2-(menthoxy)-acetylamino]-phenoxy}-benzoic acid methyl ester (3.7 g,

97%). To a solution of 4-{4-Amino-3-[2-(menthoxy)-acetylamino]-phenoxy}-benzoic acid methyl ester (400 mg) in dioxane (25 mL) was added 6 N HCl (25 mL). The mixture was kept at refluxing for about 20 h, then cooled to 0 °C, quenched with 10% NaOH, extracted with EtOAc (3X30 mL), and washed with brine (2x15 mL). The organic layer was dried over Na_2SO_4, and was concentrated to give crude product, which was purified further by prep HPCL to give 4-[2-Menthoxy-1H-benzoimidazol-5-yloxy]-benzoic acid (232 mg).

4) ^{1}H NMR (DSMO-d_6/TFA) 7.9(d, 2), 7.7 (d, 1), 7.4 (s, 1), 6.9 (d, 2), 5.0 (d, 1), 4.9 (d, 1), 3.22 (m, 1), 2.1 (m, 2), 1.5 (m, 2), 1.3 (m, 2), 0.6-0.9 (m, 10), 0.55 (d, 3).

5) Other compounds made using similar methods as described in Example 7 are as follows (^{1}H NMR data included for particularly preferred compounds):

4-[2-(Menthoxymethyl)-1-(4-trifluoromethyl-benzyl)-1H-benzoimidazol-5-yloxy]-benzoic acid [(300 MHz, DSMO-d_6/TFA): 7.8-8.0 (m, 3), 7.6 (m, 3), 7.2-7.55 (m, 4), 7.1 (d, 1), 7.0 (d, 1), 5.9 (d, 2), 5.2 (m, 1), 4.9 (m, 1), 3.3 (m, 1), 2.1 (m, 1), 1.9 (m, 1), 1.5(m, 2), 1.3 (m, 1), 1.2 (m, 1), 0.8 (d, 3), 0.7 (d, 3), 0.55 (d, 3)];

4-[1-(2-Menthoxy-ethyl)-2-(menthoxymethyl)-3H-benzoimidazol-5-yloxy]-benzoic acid [(300 MHz, DSMO-d_6/TFA): 8.0 (d, 2), 7.7(d, 1), 7.06 (s, 1), 6.8-7.0 (m, 3), 5.2 (d, 1), 5.1 (d, 1), 4.52 (m, 1), 4.4 (m, 1), 3.9 (m, 1), 3.6 (m, 1), 3.3 (m, 1), 2.9 (m, 1), 2.2 (m, 1), 2.1 (m, 1), 1.8 (m, 1), 1.4-1.7 (m, 4), 1.3 (m, 1), 1.2 (m, 1), 1.0 (m, 1), 0.6-0.95 (m, 24), 0.6 (d, 3), 0.4 (d, 3)].

Example 8

Preparation of 3-{3-[2-Menthoxy-acetylamino]-4-nitro-phenoxy}-benzoic acid

1) To a stirred solution of 3-hydroxymethylbenzoate (152 mg, 2.12 mmol) in DMF (5 mL), 60 % NaH (85.1 mg, 2.12 mmol) was added. After 20 min, N-(5-fluoro-2-nitro-phenyl)-2-(menthoxy)-acetamide (500 mg, 1.42 mmol) in DMF (5 mL) was added, and the reaction mixture was stirred at rt overnight. The reaction was quenched with water (10 mL), and extracted with EtOAc (3x15 mL). The organic layer was dried over Na_2SO_4, concentrated to give crude product.

2) To a stirred solution of the ester in THF (4 mL) and MeOH (4 mL) was added LiOH (80mg, 3.48 mmol) in H_2O (5 mL) at room temperature. The reaction was completed after 6 h at rt, and diluted with water (10 mL), acidified with 1 N HCl to pH 5~6, and extracted with EtOAc (3x20 mL). The organic layer was dried over Na_2SO_4, and concentrated to afford crude

product. Purification by prep-HPLC to afford 3-{3-[2-Menthoxy-acetylamino]-4-nitro-phenoxy}-benzoic acid (51 mg) as a yellow solid.

3) ^{1}H NMR (300 MHz, DMSO), 11.3 (s, 1), 8.27 (m, 2), 7.84 (s, 1), 7.62 (m, 2), 7.47 (s, 1), 6.89 (m, 1), 4.12 (m, 4), 3.12 (m, 1), 1.1~2.3 (m, 9), 0.92 (d, 6), 0.74 (d, 3).

4) Other compounds made using similar methods as described in Example 8 are as follows:

4-{3-[2-Menthoxy-acetylamino]-phenoxymethyl}-benzoic acid;

N-[3-(2-Hydroxy-5-nitro-benzyloxy)-phenyl]-2-menthoxy-acetamide;

4-{3-[2-Menthoxy-acetylamino]-phenoxymethyl}-3-methoxy-benzoic acid;

2-Menthoxy-N-{3-[4-(1H-tetrazol-5-yl)-benzyloxy]-phenyl}-acetamide;

4-{4-(3-Carboxy-propionylamino)-3-[2-menthoxy-acetylamino]-phenoxy}-benzoic acid methyl ester;

4-{4-Isobutyrylamino-3-[2-menthoxy-acetylamino]-phenoxy}-benzoic acid;

4-{3-[2-Menthoxy-acetylamino]-4-nitro-phenoxy}-benzoic acid;

4-{4-Ethoxycarbonylamino-3-[2-menthoxy-acetylamino]-phenoxy}-benzoic acid;

6-{3-[2-Menthoxy-acetylamino]-4-nitro-phenoxy}-nicotinic acid;

6-{3-[2-Menthoxy-acetylamino]-phenoxy}-nicotinic acid;

4-{3,4-Bis-[2-menthoxy-acetylamino]-phenoxymethyl}-benzoic acid;

4-{3-[2-Menthoxy-acetylamino]-2-nitro-phenoxy}-benzoate;

4-{4-(4-Hexyloxy-benzoylamino)-3-[2-menthoxy-acetylamino]-phenoxy}-benzoic acid.

Example 9

Preparation of 1-{3-[2-Menthoxy-acetylamino]-4-nitro-phenyl}-piperidine-4-carboxylic acid

1) A solution of N-(5-fluoro-2-nitro-phenyl)-2-(menthoxy)-acetamide (500 mg, 1.42 mmol), isonipecotic acid (220 mg, 1.7 mmol), and DIEA (0.3 mL) in DSMO (15 mL) was stirred at 70 °C for 5 h. The yellow suspension was cooled to rt, diluted with ice-water (50 mL), acidified with 5% HCl to pH 5~ 6, and extracted with EtOAc (3x40 mL). The organic layer was dried over Na_2SO_4, and concentrated to afford crude product. Purification by prep-HPLC to afford 1-{3-[2-Menthoxy-acetylamino]-4-nitro-phenyl}-piperidine-4-carboxylic acid (441mg, 68%) as a yellow solid.

2) ^{1}H NMR (300 MHz, DMSO-d_6) 11.5 (br s, 1), 8.2 (br s, 1), 8.1 (d, 1), 6.8 (d, 1), 4.1 (AB q, 2), 3.8 (d, 2), 3.1 (t, 3), 2.6 (m, 1), 2.3 (m, 1), 2.1 (m, 1), 1.9 (m, 2), 1.5 (m, 4),1.3 (m, 2), 0.9 (m, 12).

3) Other compounds made using similar methods as described in Example 9 are as follows (^{1}H NMR data included for particularly preferred compounds):

1 -{3-[2-Menthoxy-acetylamino]-4-nitro-phenyl}-pyrrolidine-2-carboxylic acid [(300 MHz, $CDCl_3$) 11.9 (s, 1), 8.2 (d, 1), 8.1 (s, 1), 6.5 (br s, 1), 6.3 (d, 1), 4.2 (d, 1), 4.2 (m, 2), 3.7 (m, 1), 3.5 (m, 1), 3.2 (m, 1), 2.2 (m, 6), 1.6 (m, 2), 1.4 (m, 2), 0.9 (m, 12)];

1-{3-[2-Menthoxy-acetylamino]-4-nitro-phenyl}-piperidine-3-carboxylic acid [(300 MHz, DMSO-d_6) 11.5 (br s, 1), 8.2 (br s, 1), 8.1 (d, 1), 6.8 (d, 1), 4.1 (AB q, 2), 3.9 (d, 1), 3.7 (d, 1), 3.2 (m, 3), 2.1 (m, 3), 1.6 (m, 5), 1.3 (m, 2), 0.8 (m, 13)];

1-{3,4-Bis-[2-menthoxy-acetylamino]-phenyl}-piperidine-4-carboxylic acid [(400 MHz, DMSO-d_6): 9.2 (d, 2), 7.4 (m, 2), 7.0 (d, 1), 4.0 (m, 6), 3.5 (d, 2), 3.2 (t, 2), 3.0 (t, 2), 2.1 (m, 6), 1.6 (m, 6), 1.3 (m, 4), 0.8 (m, 23)];

1-{3-[2-Menthoxy-acetylamino]-4-nitro-phenyl}-azetidine-3-carboxylic acid;

1-[3-[2-Menthoxy-acetylamino]-4-(4-trifluoromethyl-benzoylamino)-phenyl]-piperidine-4-carboxylic acid;

1-{3-[2-Menthoxy-acetylamino]-4-[(naphthalene-1-carbonyl)-amino]-phenyl}-piperidine-4-carboxylic acid;

1-{3-[2-Menthoxy-acetylamino]-4-phenylacetylamino-phenyl}-piperidine-4-carboxylic acid;

1 -{3-[2-Menthoxy-acetylamino]-4-nitro-phenyl}-piperidine-2-carboxylic acid.

Example 10

Preparation of 1-[6-[2-Menthoxy-ethylamino]-5-nitro-pyridin-2-yl]-piperidine-4-carboxylic acid

1) To a stirred solution of Menthoxyacetyl chloride (10 g, 43 mmol) in THF (200 mL) was added concentrated ammonium hydroxide (10 mL) at rt. After 1 h, the reaction mixture was concentrated to dryness, and the resulting residue was diluted with EtOAc (300 mL), and washed with brine (2x100 mL). The organic layer was dried over Na_2SO_4, concentrated to give crude product. The crude product was dissolved in diethyl ether (100 mL), and was added drop-wise to a suspension of $LiAlH_4$ (4 g, 105 mmol) in ether (200 mL). The reaction mixture was kept at reflux for about 3 h, then cooled to 0 °C, and quenched with 50% NaOH (15 mL).

Filtered off solid through Celite, and the filtrate was concentrated to give crude product, which was purified by flash chromatography to give 2-(Menthoxy)-ethylamine (7 g, 82%).

2) To a stirred solution of 2,6-dichloro-3-nitropyridine (5.81 g, 30.1 mmol) in acetonitrile (200 mL) was added triethyl amine (6.1 g, 60.2 mmol) and 2-(Menthoxy)-ethylamine (6 g, 30.1 mmol). The reaction was stirred at rt overnight, and was quenched with brine (150 mL), extracted with EtOAc (3x100 mL), washed with brine (3x30 mL). The organic layer was dried over Na_2SO_4, concentrated to give crude product, which was purified further by flash chromatography to give product (6-chloro-3-nitro-pyridin-2-yl)-2-(menthoxy)-ethyl]-amine (9.2 g, 92%).

3) A mixture of isonipecotic acid (129 mg, 1 mmol), (6-chloro-3-nitro-pyridin-2-yl)-2-(menthoxy)-ethyl]-amine (360 mg, 1 mmol), and K_2CO_3 (276 mg, 2 mmol) in DMSO (5 mL) was stirred at rt overnight. The reaction was quenched with 5% HCl to pH 5~6, and extracted with EtOAc (3x15 mL), washed with brine (2x5 mL). The organic layer was dried over Na_2SO_4, concentrated to give crude product, which was purified further by prep-HPLC to give 1-[6-[2-Menthoxy-ethylamino]-5-nitro-pyridin-2-yl]-piperidine-4-carboxylic acid.

4) ^{1}H NMR(300 MHz, DSMO-d_6/TFA) 8.82 (m, 1), 8.03 (d, 1), 6.26 (m, 1), 3.7 (m, 1), 3.62 (br, 2), 3.43 (m, 1), 3.12 (m, 2), 3.0 9m, 1), 2.56 (m, 1), 2.1 (m, 1), 2.0 (m, 1), 1.92 (m, 2), 1.41-1.63 (m, 4), 1.3 (br, 10, 1.1 (m, 1), 0.78 (m, 4), 0.7 (d, 3), 0.68 (m, 1), 0.6 (d, 3).

5) Other compounds made using similar methods as described in Example 10 are as follows (^{1}H NMR data included for particularly preferred compounds):

1-{6-[2-Menthoxy-ethylamino]-5-nitro-pyridin-2-yl}-pyrrolidine-2-carboxylic acid [(300 MHz, DSMO-d_6/TFA) 8.7 (m, 1), 8.1 (d, 1), 6.1 (d, 1), 4.4 (m, 1), 3.3-3.75 (m, 5), 3.0 (m, 1), 2.2 (m, 1), 2.1 (m, 1), 1.9 (m, 3), 1.5 (m, 2), 1.3 (m, 1), 1.1 (m, 1), 0.6-0.9 (m, 8), 0.55 (d, 3)];

4-{6-[2-Menthoxy-ethylamino]-5-nitro-pyridin-2-yloxy}-3-morpholin-4-ylmethyl-benzoic acid [(300 MHz, DSMO-d_6/TFA) 8.7 (m, 1), 8.55 (d, 1), 8.3 (s, 1), 8.0 (d, 1), 7.43 (d, 1), 6.6 (d, 1), 4.3 (br, 2), 3.7 (m, 4), 3.4 (m, 1), 3.2 (m, 4), 2.9 (m, 1), 2.0 (m, 2), 1.6 (m, 1), 1.5 (m, 1), 1.3 (m, 1), 1.1 (m, 1), 0.8 (s, 3), 0.7 (d, 3), 0.65 (m, 1), 0.6 (d, 3)];

1-[6-[2-Menthoxy-ethylamino]-5-nitro-pyridin-2-yl]-piperidine-3-carboxylic acid [(300 MHz, DSMO-d_6/TFA): 8.75 (m, 1), 8.0 (d, 1), 6.3 (d, 1), 3.75 (m, 1), 3.6 (m, 2), 3.2-3.6 (m, 3), 2.4 (m, 1), 2.1 (m, 1), 1.9 (m, 1), 1.7 (m, 2), 1.5 (m, 3), 1.3 (m, 1), 1.1 (m, 1), 0.6-0.9 (m, 8), 0.55 (d, 3)];

4-{6-[2-Menthoxy-ethylamino]-5-nitro-pyridin-2-ylamino}-cyclohexanecarboxylic acid [(300 MHz, DSMO-d_6/TFA): 8.61 (m, 1), 8.4 (d, 1), 8.12 (m, 1), 6.78 (d, 1), 5.7 (br, 1), 3.55-3.81 (m, 4), 3.4 (m, 3), 3.1 (m, 1), 2.04 (m, 4), 1.40-1.67 (m, 4), 1.3 (m, 2), 1.06 (m, 2), 1.11-1.37 (m, 2), 0.65-0.91 (m, 7), 0.59 (d, 3).

Example 11

Preparation of 4-{6-[2-Menthoxy-ethylamino]-5-nitro-pyridin-2-yloxy}-benzoic acid

1) To a stirred solution of 4-hydroxybenzoic acid (138 mg, 1 mmol) in DMSO (5 mL), K_2CO_3 (276 mg, 2 mmol) was added. After 20 min, (6-chloro-3-nitro-pyridin-2-yl)-2-(menthoxy)-ethyl]-amine in DMF (5 mL) was added, and the reaction mixture was stirred at rt overnight. The reaction was quenched with 5% HCl to pH 5~6, and extracted with EtOAc (3x15 mL). The organic layer was dried over Na_2SO_4, concentrated to give crude product, which was purified further by prep-HPLC to give product 4-{6-[2-Menthoxy-ethylamino]-5-nitro-pyridin-2-yloxy}-benzoic acid (110 mg, 24%).

2) ^{1}H NMR (300 MHZ, DSMO-d_6/TFA) 8.63 (m, 1), 8.42 (d, 1), 8.0 (d, 2), 7.4 (d, 2), 6.4 (d, 1), 3.55 (m, 1), 3.3-3.5 (m, 4), 3.2 (m, 1), 2.8 (m, 1), 2.0 (m, 1), 1.9 (m, 1), 1.55 (m, 1), 1.42 (m, 1), 1.3 (m, 1), 1.0 (m, 1), 0.75-0.9 (m, 4), 0.7 (d, 3), 0.6 (m, 1), 0.5 (d, 3)

3) Other compounds made using similar methods as described in Example 11 are as follows (^{1}H NMR data included for particularly preferred compounds):

4-{5-[2-Menthoxy-ethoxy]-2-nitro-phenoxy}-benzoic acid;

4-{6-[2-Menthoxy-ethylamino]-5-nitro-pyridin-2-yloxy}-benzoic acid [(300 MHz, DSMO-d_6/TFA 8.63 (m, 1), 8.42 (d, 1), 8.0 (d, 2), 7.4 (d, 2), 6.4 (d, 1), 3.55 (m, 1), 3.3-3.5 (m, 4), 3.2 (m, 1), 2.8 (m, 1), 2.0 (m, 1), 1.9 (m, 1), 1.55 (m, 1), 1.42 (m, 1), 1.3 (m, 1), 1.0 (m, 1), 0.75-0.9 (m, 4), 0.7 (d, 3), 0.6 (m, 1), 0.5 (d, 3)].

Example 12

Preparation of Representative Pharmaceutical Compositions for Oral Administration

This example illustrates the preparation of representative pharmaceutical compositions for oral administration containing a compound of the present invention, or a pharmaceutically acceptable salt thereof, e.g., 3-Hydroxy-4-[(4-{[2-menthoxy-acetylamino] methyl}-phenylamino)-methyl]-8-methoxy-1,9-dimethyl-11-oxo-11H-dibenzo[b,e][1,4]dioxepine-6-carboxylic acid:

1.	Ingredients	% wt./wt.
	Compound of the invention	20.0%
	Lactose	79.5%
	Magnesium stearate	0.5%

The above ingredients are mixed and dispensed into hard-shell gelatin capsules containing 100 mg each, one capsule would approximate a total daily dosage.

2.	Ingredients	% wt./wt.
	Compound of the invention	20.0%
	Magnesium stearate	0.9%
	Starch	8.6%
	Lactose	69.6%
	PVP (polyvinylpyrrolidine)	0.9%

The above ingredients, with the exception of the magnesium stearate, are combined and granulated using water as a granulating liquid. the formulation is then dried, mixed with the magnesium stearate and formed into tablets with an appropriate tableting machine.

3.	Ingredients	% wt./wt.
	Compound of the invention	0.1 g
	Propylene glycol	20.0 g
	Polyethylene glycol 400	20.0 g
	Polysorbate 80	1.0 g
	Water	q.s. 100 mL

The compound of the invention is dissolved in propylene glycol, polyethylene glycol 400 and polysorbate 80. A sufficient quantity of water is then added with stirring to provide 100 mL of the solution which is filtered and bottled.

4.	Ingredients	% wt./wt.
	Compound of the invention	20.0%
	Peanut oil	78.0%
	Span 60	2.0%

The above ingredients are melted, mixed and filled into soft elastic capsules.

5.	Ingredients	% wt./wt.
	Compound of the invention	1.0%
	Methyl or carboxymethyl cellulose	2.0%
	0.9% saline	q.s. 100 mL

The compound of the invention is dissolved in the cellulose/saline solution, filtered and bottled for use.

Example 13

Preparation of Representative Pharmaceutical Compositions for Parenteral Administration

This example illustrates the preparation of a representative pharmaceutical formulation for parenteral administration containing a compound of the invention, or a pharmaceutically acceptable salt thereof, e.g., 3-Hydroxy-4-[(4-{[2-menthoxy-acetylamino] methyl}-phenylamino)-methyl]-8-methoxy-1,9-dimethyl-11-oxo-11H-dibenzo[b,e][1,4]dioxepine-6-carboxylic acid:

Ingredients	% wt./wt.
Compound of the invention	0.02 g
Propylene glycol	20.0 g
Polyethylene glycol 400	20.0 g
Polysorbate 80	1.0 g
0.9% saline solution	q.s. 100 mL

The compound of the invention is dissolved in propylene glycol, polyethylene glycol 400 and polysorbate 80. A sufficient quantity of 0.9% saline solution is then added with stirring to provide 100 mL of the I.V. solution which is filtered through a 0.2μ membrane filter and packaged under sterile conditions.

Example 14

Preparation of Representative Pharmaceutical Compositions in Suppository Form

This example illustrates the preparation of a representative pharmaceutical composition in suppository form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, e.g., 3-Hydroxy-4-[(4-{[2-menthoxy-acetylamino] methyl}-phenylamino)-methyl]-8-methoxy-1,9-dimethyl-11-oxo-11H-dibenzo[b,e][1,4]dioxepine-6-carboxylic acid:

Ingredients	% wt./wt.
Compound of the invention	1.0%
Polyethylene glycol 1000	74.5%
Polyethylene glycol 4000	24.5%

The ingredients are melted together and mixed on a steam bath, and poured into molds containing 2.5 g total weight.

Example 15

Preparation of Representative Pharmaceutical Compositions for Insufflation

This example illustrates the preparation of a representative pharmaceutical formulation for insufflation containing a compound of the invention, or a pharmaceutically acceptable salt thereof, e.g., 3-Hydroxy-4-[(4-{[2-menthoxy-acetylamino] methyl}-phenylamino)-methyl]-8-methoxy-1,9-dimethyl-11-oxo-11H-dibenzo[b,e][1,4]dioxepine-6-carboxylic acid:

Ingredients	% wt./wt.
Micronized compound of the invention	1.0%
Micronized lactose	99.0%

The ingredients are milled, mixed, and packaged in an insufflator equipped with a dosing pump.

Example 16

Preparation of Representative Pharmaceutical Compositions in Nebulized Form

This example illustrates the preparation of a representative pharmaceutical formulation in nebulized form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, e.g., 3-Hydroxy-4-[(4-{[2-menthoxy-acetylamino] methyl}-phenylamino)-methyl]-8-methoxy-1,9-dimethyl-11-oxo-11H-dibenzo[b,e][1,4]dioxepine-6-carboxylic acid:

Ingredients	% wt./wt.
Compound of the invention	0.005%
Water	89.995%
Ethanol	10.000%

The compound of the invention is dissolved in ethanol and blended with water. The formulation is then packaged in a nebulizer equipped with a dosing pump.

Example 17

Preparation of Representative Pharmaceutical Compositions in Aerosol Form

This example illustrates the preparation of a representative pharmaceutical formulation in aerosol form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, e.g., 3-Hydroxy-4-[(4-{[2-menthoxy-acetylamino] methyl}-phenylamino)-methyl]-8-methoxy-1,9-dimethyl-11-oxo-11H-dibenzo[b,e][1,4]dioxepine-6-carboxylic acid:

Ingredients	% wt./wt.
Compound of the invention	0.10%
Propellant 11/12	98.90%
Oleic acid	1.00%

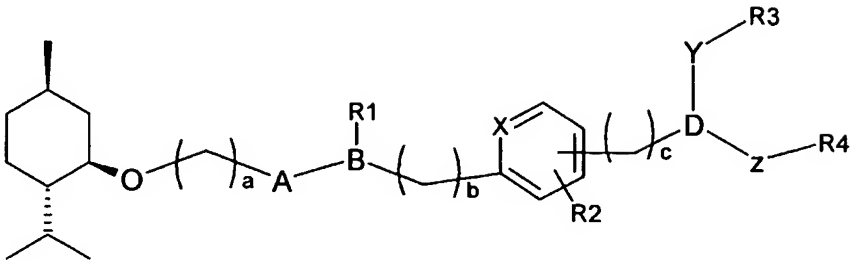
The compound of the invention is dispersed in oleic acid and the propellants. The resulting mixture is then poured into an aerosol container fitted with a metering valve.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes and modifications may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims as appended hereto.

Claims

What is claimed is:

1. A compound of the following formula:



wherein:

a, b, and c is 0 to 2;

A is either absent or present and is either carbonyl or forms a heterocyclic ring system with B (if B is N) and the phenyl group;

B is either absent or present and is selected from the group consisting of N or O;

R1 is either absent or present and is selected from the group consisting of hydrogen, alkyl, alkylene, aryl, haloalkyl, menthoxy alkyl, or forms a heterocyclic ring system with the N and the phenyl (preferably forming an optionally substituted indole);

R2 is selected from the group consisting of hydrogen, alkoxy, amino, monoalkylaminocarbonyl, monoalkylaminocarbonyl carboxylic acid, nitro, alkyl, haloalkyl, substituted aralkoxy (substituted with carboxylic acid), alkoxy substituted phenyl amido, cyclohexyloxybenzoylamino, or a fused [1,3]dioxinyl ring system with the phenyl;

X is either C or N;

D is either absent or present and is either O or N;

Y is either absent or present and is selected from alkylene, aryl, carbonyl, or forms a heterocyclic ring system with D (if D is N) and the phenyl ring;

Z is either absent or present and is selected from the group consisting of alkylene, sulfonyl, aminocarbonyl, or carbonyl;

R3 is either absent or present and is selected from the group consisting of optionally substituted phenyl (optionally substituted by hydrogen, nitro, hydroxy, and/or alkoxy), carboxylic acid, alkoxy, alkyl or carbamate ester; and

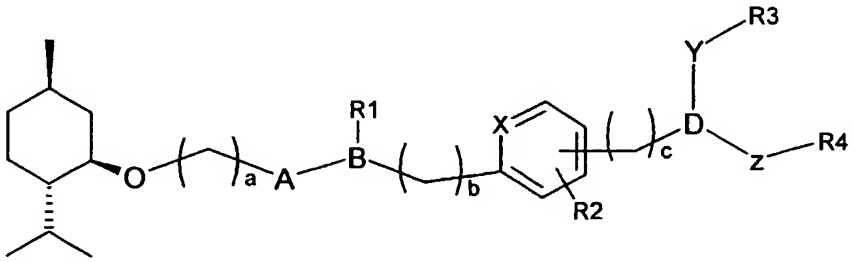
R4 is either absent or present and is selected from the group consisting of optionally substituted dibenzo[b,e][1,4]dioxepin-11-one (wherein said phenyl groups of said dioxepinone are optionally substituted by hydroxy, alkyl, carboxylic acid, and alkoxy), optionally

substituted pyridinyl (optionally substituted by carboxylic acid and/or alkylene), naphthalene, optionally substituted phenyl (optionally substituted by one or more of hydroxy, carboxylic acid, nitro, alkyl, alkoxy, carboxylic acid substituted alkoxy, alkyl ester, acetic acid, acetic acid ether, amido, amino, alkoxyamido, methanesulfonyl amino, halo, tetrazolyl, optionally substituted aralkoxy (optionally substituted by hydroxy, carboxylic acid, nitro, alkyl, alkoxy, tetrazolyl), optionally substituted aryloxy (optionally substituted one or more times by hydroxy, carboxylic acid, nitro, alkyl, alkoxy, tetrazolyl, carboxylic acid substituted alkoxy, alkyl ester, amino, halo, or aryloxy), carboxylic acid substituted phenyl ester, optionally substituted piperazinyl (optionally substituted by carboxylic acid or carboxylic acid substituted alkoxy, alkyl ester), optionally substituted pyridinyloxy (optionally substituted by carboxylic acid, carboxylic acid alkyl ester, or cyano), carboxylic acid substituted cyclohexyl, or optionally substituted fully saturated monocyclic aza ring with up to six carbon atoms (optionally substituted by carboxylic acid alkyl ester or carboxylic acid)), alkoxy, carboxylic acid substituted cyclohexane, or carboxylic acid substituted fully saturated monocyclic aza ring with up to six carbon atoms; or

R3 and R4 form a carboxylic acid substituted fully saturated monocyclic aza ring with up to 6 carbon atoms,

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

2. A pharmaceutical composition useful in treating a human having a disease-state characterized by thrombotic activity, which composition comprises a therapeutically effective amount of a compound of the following formula:



wherein:

a, b, and c is 0 to 2;

A is either absent or present and is either carbonyl or forms a heterocyclic ring system with B (if B is N) and the phenyl group;

B is either absent or present and is selected from the group consisting of N or O;

R1 is either absent or present and is selected from the group consisting of hydrogen, alkyl, alkylene, aryl, haloalkyl, menthoxy alkyl, or forms a heterocyclic ring system with the N and the phenyl (preferably forming an optionally substituted indole);

R2 is selected from the group consisting of hydrogen, alkoxy, amino, monoalkylaminocarbonyl, monoalkylaminocarbonyl carboxylic acid, nitro, alkyl, haloalkyl, substituted aralkoxy (substituted with carboxylic acid), alkoxy substituted phenyl amido, cyclohexyloxybenzoylamino, or a fused [1,3]dioxinyl ring system;

X is either C or N;

D is either absent or present and is either O or N;

Y is either absent or present and is selected from alkylene, aryl, carbonyl, or forms a heterocyclic ring system with D (if D is N) and the phenyl ring;

Z is either absent or present and is selected from the group consisting of alkylene, sulfonyl, aminocarbonyl, or carbonyl;

R3 is either absent or present and is selected from the group consisting of optionally substituted phenyl (optionally substituted by hydrogen, nitro, hydroxy, and/or alkoxy), carboxylic acid, alkoxy, alkyl or carbamate ester; and

R4 is either absent or present and is selected from the group consisting of optionally substituted dibenzo[b,e][1,4]dioxepin-11-one (wherein said phenyl groups of said dioxepinone are optionally substituted by hydroxy, alkyl, carboxylic acid, and alkoxy), optionally substituted pyridinyl (optionally substituted by carboxylic acid and/or alkylene), naphthalene, optionally substituted phenyl (optionally substituted by one or more of hydroxy, carboxylic acid, nitro, alkyl, alkoxy, carboxylic acid substituted alkoxy, alkyl ester, acetic acid, acetic acid ether, amido, amino, alkoxyamido, methanesulfonyl amino, halo, tetrazolyl, optionally substituted aralkoxy (optionally substituted by hydroxy, carboxylic acid, nitro, alkyl, alkoxy, tetrazolyl), optionally substituted aryloxy (optionally substituted one or more times by hydroxy, carboxylic acid, nitro, alkyl, alkoxy, tetrazolyl, carboxylic acid substituted alkoxy, alkyl ester, amino, halo, or aryloxy), carboxylic acid substituted phenyl ester, optionally substituted piperazinyl (optionally substituted by carboxylic acid or carboxylic acid substituted alkoxy, alkyl ester), optionally substituted pyridinyloxy (optionally substituted by carboxylic acid, carboxylic acid alkyl ester, or cyano), carboxylic acid substituted cyclohexyl, or optionally substituted fully saturated monocyclic aza ring with up to six carbon atoms (optionally

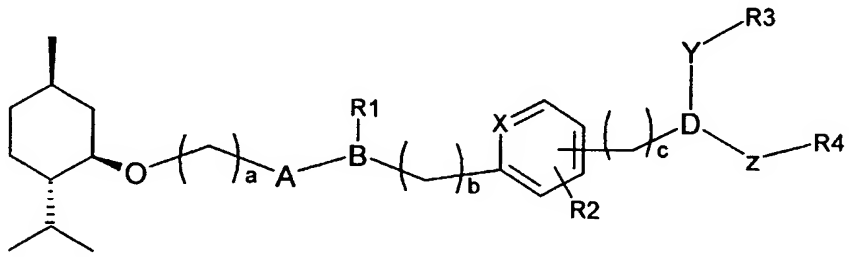
substituted by carboxylic acid alkyl ester or carboxylic acid)), alkoxy, carboxylic acid substituted cyclohexane, or carboxylic acid substituted fully saturated monocyclic aza ring with up to six carbon atoms; or

R3 and R4 form a carboxylic acid substituted fully saturated monocyclic aza ring with up to 6 carbon atoms,

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

3. The pharmaceutical composition of claim 2 wherein the disease-state is selected from the group consisting of unstable angina, myocardial infarction, cerebral thromboembolism, transient ischemic attack, stroke, DVT, and coronory reocclusion after thrombolytic therapy.

4. A method of treating a human having a disease-state characterized by thrombotic activity, which method comprises administering to a human in need thereof a therapeutically effective amount of a compound of the following formula:



wherein:

a, b, and c is 0 to 2;

A is either absent or present and is either carbonyl or forms a heterocyclic ring system with B (if B is N) and the phenyl group;

B is either absent or present and is selected from the group consisting of N or O;

R1 is either absent or present and is selected from the group consisting of hydrogen, alkyl, alkylene, aryl, haloalkyl, menthoxy alkyl, or forms a heterocyclic ring system with the N and the phenyl (preferably forming an optionally substituted indole);

R2 is selected from the group consisting of hydrogen, alkoxy, amino, monoalkylaminocarbonyl, monoalkylaminocarbonyl carboxylic acid, nitro, alkyl, haloalkyl, substituted aralkoxy (substituted with carboxylic acid), alkoxy substituted phenyl amido, cyclohexyloxybenzoylamino, or a fused [1,3]dioxinyl ring system;

X is either C or N;

D is either absent or present and is either O or N;

Y is either absent or present and is selected from alkylene, aryl, carbonyl, or forms a heterocyclic ring system with D (if D is N) and the phenyl ring;

Z is either absent or present and is selected from the group consisting of alkylene, sulfonyl, aminocarbonyl, or carbonyl;

R3 is either absent or present and is selected from the group consisting of optionally substituted phenyl (optionally substituted by hydrogen, nitro, hydroxy, and/or alkoxy), carboxylic acid, alkoxy, alkyl or carbamate ester; and

R4 is either absent or present and is selected from the group consisting of optionally substituted dibenzo[b,e][1,4]dioxepin-11-one (wherein said phenyl groups of said dioxepinone are optionally substituted by hydroxy, alkyl, carboxylic acid, and alkoxy), optionally substituted pyridinyl (optionally substituted by carboxylic acid and/or alkylene), naphthalene, optionally substituted phenyl (optionally substituted by one or more of hydroxy, carboxylic acid, nitro, alkyl, alkoxy, carboxylic acid substituted alkoxy, alkyl ester, acetic acid, acetic acid ether, amido, amino, alkoxyamido, methanesulfonyl amino, halo, tetrazolyl, optionally substituted aralkoxy (optionally substituted by hydroxy, carboxylic acid, nitro, alkyl, alkoxy, tetrazolyl), optionally substituted aryloxy (optionally substituted one or more times by hydroxy, carboxylic acid, nitro, alkyl, alkoxy, tetrazolyl, carboxylic acid substituted alkoxy, alkyl ester, amino, halo, or aryloxy), carboxylic acid substituted phenyl ester, optionally substituted piperazinyl (optionally substituted by carboxylic acid or carboxylic acid substituted alkoxy, alkyl ester), optionally substituted pyridinyloxy (optionally substituted by carboxylic acid, carboxylic acid alkyl ester, or cyano), carboxylic acid substituted cyclohexyl, or optionally substituted fully saturated monocyclic aza ring with up to six carbon atoms (optionally substituted by carboxylic acid alkyl ester or carboxylic acid)), alkoxy, carboxylic acid substituted cyclohexane, or carboxylic acid substituted fully saturated monocyclic aza ring with up to six carbon atoms; or

R3 and R4 form a carboxylic acid substituted fully saturated monocyclic aza ring with up to 6 carbon atoms,

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

5. The method of claim 4 wherein the disease-state is selected from the group consisting of unstable angina, myocardial infarction, cerebral thromboembolism, transient ischemic attack, stroke, DVT, and coronary reocclusion after thrombolytic therapy.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/07506

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C235/06 C07C235/16 C07D235/12 C07D211/60 A61K31/165
A61K31/167 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 4745018 XP002250240 abstract & UMEMOTO, T ET AL: BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN., vol. 64, no. 4, 1991, pages 1081-1092, JAPAN PUBLICATIONS TRADING CO. TOKYO., JP ISSN: 0009-2673 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 August 2003	21/08/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	O'Sullivan, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/07506

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 17185 XP002250241 abstract & RULE ET AL: JOURNAL OF THE CHEMICAL SOCIETY., 1931, pages 1478-1481, CHEMICAL SOCIETY, LONDON, GB ISSN: 0368-1769 ---	1
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 6656515 XP002250242 abstract & CHONG, J. M. ET AL: JOURNAL OF ORGANIC CHEMISTRY., vol. 58, no. 25, 1993, pages 7300-7303, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0022-3263 ---	1
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 3206656 XP002250243 abstract & HUECKEL, K ET AL: CHEMISCHE BERICHTE., vol. 91, 1958, pages 311-319, VERLAG CHEMIE GMBH. WEINHEIM., DE ISSN: 0009-2940 ---	1
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 3200940 XP002250244 abstract & RULE, T: JOURNAL OF THE CHEMICAL SOCIETY., 1931, pages 1929-1933, CHEMICAL SOCIETY, LONDON, GB ISSN: 0368-1769 ---	1

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 3143538 XP002250245 abstract & FORSTER ET AL: JOURNAL OF THE CHEMICAL SOCIETY., vol. 99, 1911, page 1339 CHEMICAL SOCIETY, LONDON, GB ISSN: 0368-1769 ---	1
X	BRIMBLE M A ET AL: "Addition of Cyclopentadiene and 2-Trimethylsilyloxyfuran to Quinones Bearing a Menthyl Ester Chiral Auxiliary" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 54, no. 20, 14 May 1998 (1998-05-14), pages 5363-5374, XP004116437 ISSN: 0040-4020 scheme 2, compound 7 ---	1
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 3750786 XP002250246 abstract & KISSMAN, T: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 74, 1952, page 4317 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 ---	1
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 3175857 XP002250247 abstract & KISSMAN, T: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 74, 1952, page 4317 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 --- -/--	1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/07506

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 3156332 XP002250248 abstract & HOLMES; ADAMS: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 56, 1934, page 2093 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863	1
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; retrieved from 3147711 XP002250249 abstract & KISSMAN, T: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 74, 1952, page 4317 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863	1
P,X	WO 03 002519 A (FAESTE CHRISTIANE ;PERNERSTORFER JOSEF (DE); VOEHRINGER VERENA (DE) 9 January 2003 (2003-01-09) page 32, line 4 - line 12 example 125	2-5
A	US 6 121 308 A (ZIMMERMANN RAINER ET AL) 19 September 2000 (2000-09-19) claim 1	1-5
A	US 5 494 921 A (EGBERTSON MELISSA S ET AL) 27 February 1996 (1996-02-27) column 1, line 1 - line 25 column 13-19, compounds column 35, line 60 -column 36, line 19	1-5
A	WO 01 79193 A (CORVAS INT INC ;ARALDI GIAN LUCA (US); SEMPLE JOSEPH EDWARD (US)) 25 October 2001 (2001-10-25) page 1, line 9 - line 19 page 121; example 38	1-5

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Regarding: Claim 1

The initial phase of the search revealed a very large number of documents relevant to the issue of the novelty of compound claim 1. So many documents were retrieved that it is impossible to determine which parts of claim 1 may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim 1 is impossible. Some representative documents featuring the compounds of unrestricted claim 1 have been cited X in the Search Report (citations 1-7). Consequently, the Search Report may only be considered complete for the compounds of the preferred subgroups listed in the description on pages 17, 20-22 and 25-29, namely compounds of the formulae IA, IA1, IA2, IB, IB1, IB2, IB3, IB4, IC and ID.

Note: the Search Report may be considered complete for claims 2-5.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/07506

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 4-5 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/07506

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 03002519 A1	09-01-2003
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US 5494921 A	27-02-1996	AU 689961 B2	09-04-1998
		AU 3630795 A	29-03-1996
		CA 2198478 A1	21-03-1996
		EP 0781133 A1	02-07-1997
		JP 10505837 T	09-06-1998
		WO 9608250 A1	21-03-1996
WO 0179193 A	25-10-2001	US 6506760 B1	14-01-2003
		US 6506761 B1	14-01-2003
		AU 5541001 A	30-10-2001
		WO 0179193 A2	25-10-2001